INTERNATIONAL RECORD OF MEDICINE

VOLUME 170 NO. 2 | FEBRUARY 1957

ORIGINALLY PUBLISHED AS AMERICAN MEDICAL INTELLIGENCER, FOUNDED PHILADELPHIA, 1837

The Use of Pipradrol in the Problems of Obesity — Irving B. Perlstein

Topical and Oral Prednisolone in the Treatment of Dermatoses — Milton B. Sloane

The Location of Action of Chlorpromazine in the Central Nervous System — Mirko Carreras and Franco Angeleri

Value of a Therapeutic Trial with Liothyronine — Albert H. Helm

I Dreamed that I Dreamed — Nandor Fodor

Medical Instruments Section:
Modern Cancer Cell Screening Technique — H. E. Nieburgs

Editorial Survey: Humpty Dumpty on Writing

Book Reviews

International Clinical Newsletter

Advanced Reports from Current Medical Meetings

A JOURNAL OF MD PUBLICATIONS, INC.

MATROMYCIN

BRAND OF OLEANDOMYCIN

a new antibiotic to protect patients against infection or superinfection due to resistant staphylococci, particularly in hospitals where resistance is a problem and the causative agent can be determined

"Of 140 strains of *Staphylococcus aureus* isolated from patients [in children's wards], 22 were found to be . . . markedly resistant . . . to erythromycin and in each instance the organism was either quite sensitive or moderately sensitive to [Matromycin]."[1]

outstandingly effective and well tolerated in oral dosages

In a series of children with bacterial pneumonia, Matromycin achieved a "quite favorable" therapeutic effect; in the same hospital, "thirteen children with possible *Staphylococcus* enteritis responded readily to [Matromycin]." In all the cases, Matromycin produced "no demonstrable toxic effects."[1]

Capsules, 250 mg.; bottles of 16.

1. Ross, S.: Antibiotics Annual 1955-1956. New York, Medical Encyclopedia, Inc., 1956, p. 600.

Pfizer PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.

INTERNATIONAL RECORD OF MEDICINE

ORIGINALLY PUBLISHED AS AMERICAN MEDICAL INTELLIGENCER, FOUNDED PHILADELPHIA, 1837

A JOURNAL OF ADVANCED EXPERIMENTAL AND CLINICAL REPORTS

PUBLICATIONS, INC.

FELIX MARTI-IBAÑEZ, M.D., Editor-in-Chief

VOL. 170 NO. 2 *WHOLE NUMBER 2888* *FEBRUARY 1957*

The *International Record of Medicine* is published monthly by MD Publications, Inc. (30 E. 60th Street, New York, N. Y., Félix Martí-Ibáñez, M.D., President). ©Copyright 1957 by MD Publications, Inc. Entered as second class matter at the Post Office, Washington, D. C., under the Act of March 3, 1879. Matter appearing in *International Record of Medicine* is covered by copyright. The reproduction of articles (or parts of articles) appearing in *International Record of Medicine* is not permitted. Permission must be received in writing from the editor for reprinting material in whole or in part. Subscription Rate: $11.00 for one year, $28.00 for three years.

EDITORIAL BOARD

FELIX MARTI-IBAÑEZ, M.D., Editor

NATIONAL EDITORIAL BOARD

FRED L. ADAIR, M.D., *University of Chicago*

HARRY L. ARNOLD, JR., M.D., *Editor, Hawaii Medical Journal, Honolulu, Hawaii*

W. WAYNE BABCOCK, M.D., *Temple University*

HOWARD C. BALLENGER, M.D., *Northwestern University*

CONRAD BERENS, M.D., *The Ophthalmological Foundation*

ALEXANDER W. BLAIN, M.D., *Wayne University*

ALFRED BLALOCK, M.D., *Johns Hopkins University*

W. F. BRAASCH, M.D., *Mayo Clinic*

ROBERT H. BROH-KAHN, M.D., *New York, N. Y.*

MORTON S. BRYER, M.D., *The Mount Sinai Hospital*

LEROY A. CALKINS, M.D., *University of Kansas*

NORTON CANFIELD, M.D., *New Haven, Conn.*

BAYARD CARTER, M.D., *Duke University*

RUSSELL L. CECIL, M.D., *Cornell University*

F. CO TUI, M.D., *Creedmoor Institute*

FREDERICK A. COLLER, M.D., *University of Michigan*

WILLARD R. COOKE, M.D., *University of Texas*

WALTER T. DANNREUTHER, M.D., *New York University*

CLYDE L. DEMING, M.D., *Yale University School of Medicine*

R. S. DINSMORE, M.D., *Cleveland Clinic*

HENRY DOLGER, M.D., *New York, N. Y.*

I. E. DRABKIN, PH.D., *The College of the City of New York*

DANIEL C. ELKIN, M.D., *Emory University*

LUDWIG A. EMGE, M.D., *Stanford University*

HAROLD K. FABER, M.D., *Stanford University Hospital*

HARRY A. FELDMAN, M.D., *State University of New York*

JOSEPH H. FOBES, M.D., *New York Medical College*

A. STONE FREEDBERG, M.D., *Harvard Medical School, Boston, Mass.*

WILLIS D. GATCH, M.D., *University of Indiana*

LOUIS J. GELBER, M.D., *Rockville Center, L. I., N. Y.*

DAVID GROB, M.D., *Johns Hopkins Medical School*

BERNARD J. HANLEY, M.D., *University of Southern California*

FRENCH K. HANSEL, M.D., *Washington University*

CLYDE A. HEATLY, M.D., *University of Rochester*

HENRY F. HELMHOLTZ, M.D., *Mayo Clinic*

FRANK HINMAN, M.D., *University of California*

CLARENCE B. INGRAHAM, M.D., *University of Colorado*

J. BAY JACOBS, M.D., *Georgetown University*

ROBERT W. KEETON, M.D., *University of Illinois*

HARRY H. KERR, M.D., *George Washington University*

WILLIAM J. KERR, M.D., *Blue Lake, California*

I. NEWTON KUGELMASS, M.D., *New York, N. Y.*

THEODORE LIDZ, M.D., *Yale University School of Medicine*

DEAN M. LIERLE, M.D., *University of Iowa*

IRVINE MCQUARRIE, M.D., *University of Minnesota*

RALPH H. MAJOR, M.D., *University of Kansas*

ALTON OCHSNER, M.D., *Tulane University*

HENRY BOYLAN ORTON, M.D., *Newark, N. J.*

WINFRED OVERHOLSER, M.D., *George Washington University*

JAMES E. PAULLIN, M.D., *Emory University*

FRANKLIN L. PAYNE, M.D., *University of Pennsylvania*

E. D. PLASS, M.D., *University of Iowa*

TRACY J. PUTNAM, *Beverly Hills, California*

B. O. RAULSTON, M.D., *University of Southern California*

LYMAN G. RICHARDS, M.D., *Massachusetts Institute of Technology*

LEONARD G. ROWNTREE, M.D., *Miami, Fla.*

RAYMOND R. SACKLER, M.D., *New York, N. Y.*

MILTON S. SACKS, M.D., *University of Maryland School of Medicine*

MORRIS SCHAEFFER, M.D., *Director, Communicable Disease Center, Montgomery, Ala.*

LEWIS C. SCHEFFEY, M.D., *Jefferson Medical College*

SIDNEY SCHERLIS, M.D., *University of Maryland School of Medicine*

EDWARD A. SCHUMANN, M.D., *Phila., Pa.*

CYRUS C. STURGIS, M.D., *University of Michigan*

HERBERT THOMS, M.D., *Yale University*

DONALD V. TRUEBLOOD, M.D., *Seattle, Wash.*

JAMES J. WARING, M.D., *University of Colorado*

KARL M. WILSON, M.D., *University of Rochester*

FRED W. WITTICH, M.D., *Minneapolis, Minn.*

FLETCHER D. WOODWARD, M.D., *Charlottesville, Va.*

INTERNATIONAL EDITORIAL BOARD

ROMA AMYOT, M.D., *Editor-in-Chief, L'Union Medicale du Canada*

GASTON BACHELARD, M.D., *Directeur de l'Institut d'Histoire des Sciences, La Sorbonne, Paris, France*

GEOFFRY H. BATEMAN, *London, England*

PAUL DIEPGEN, M.D., *Director of Medizinhistorischen Institutes der Johannes Gutenberg Univ., Mainz, Germany*

PEDRO LAIN ENTRALGO, M.D., *Profesor de Historia de la Medicina, Madrid, Spain*

PROF. A. GIGON, *Schweizerische Akademie der Medizinischen, Wissenschaften, Basel, Switzerland*

EDV. GOTFREDSEN, M.D., *Director of the Universitetets Medicinsk-Historiske Museum, Copenhagen, Denmark*

DOUGLAS GUTHRIE, M.D., *Professor of the History of Medicine, University of Edinburgh, Edinburgh, Scotland*

WILLY HARTNER, M.D., *Johann Wolfgang Goethe Universität, Frankfurt a. M., Germany*

E. HINTZCHE, M.D., *Anatomisches Institut, Bern, Switzerland*

BJØRN IBSEN, M.D., *Chief of the Department of Anaesthesiology, Kommunehospitalet, Copenhagen, Denmark*

JUAN B. LASTRES, M.D., *Profesor de Historia de la Medicina, Universidad de San Marcos, Lima, Peru*

PROF. ADOLF MEYER-ABICH, *Elbchaussee 460, Hamburg-Blankenese, Germany*

ANDRE MOULONGUET, M.D., *Paris, France*

PROF. RODOLFO PÉREZ DE LOS REYES, *Universidad de La Habana, Cuba*

AUGUSTO PI-SUÑER, M.D., *Instituto de Medicina Experimental, Caracas, Venezuela*

ILSE ROSENTHAL-SCHNEIDER, Ph.D., *The University of Sydney, Sydney, Australia*

ANIBAL RUIZ MORENO, M.D., *Profesor de Historia de la Medicina, Buenos Aires, Argentina*

KENNETH F. RUSSELL, M.S., F.R.A.C.S., *Associate Professor of Anatomy, The University of Melbourne, Melbourne, Australia*

TH. H. SCHLICHTING, M.D., *Amsterdam, Holland*

HANS SELYE, M.D., *Université de Montréal, Montreal, Canada*

PROF. IVOLINO DA VASCONCELLOS, *President, Sociedad Brasileña de Historia da Medicina Rio de Janeiro, Brazil*

health and travel

Complete proceedings of the First Symposium on Health and Travel, held in June of 1955. Travel for the young, the old, the sick; by car, air, train, boat, and space ship; in the continental U. S., Europe, Latin America, Asia; in tropical and subtropical climes. All these problems are covered in their physiologic and psychologic aspects by top specialists in their field. The monograph includes detailed information on prophylaxis and treatment, as well as historical and entertaining general data. This attractive hard-cover book is a classic reference book for your library, as well as an attractive and much appreciated gift for a fellow physician. 72 pp. **Price: $3.00.**

contents

THE PHYSICIAN AS TRAVELER
by Félix Martí-Ibáñez, M.D., Editor-in-Chief, INTERNATIONAL RECORD OF MEDICINE & GENERAL PRACTICE CLINICS.

WHEN CHILDREN TRAVEL
by I. Newton Kugelmass, M.D., Consultant, Dept. of Health & Hospitals, New York City.

WHEN PEOPLE WHO ARE NOT YOUNG TRAVEL
by William T. Foley, M.D., Assistant Professor of Clinical Medicine & Chief of the Vascular Clinics, New York Hospital, New York City.

INFECTIONS AND TRAVEL
by Elmer H. Loughlin, M.D., Associate Clinical Professor of Medicine, New York Medical College, Flower & Fifth Avenue Hospital, New York City.

WHEN SICK PEOPLE TRAVEL
by Walter C. Alvarez, M.D., Editor-in-Chief, MODERN MEDICINE

TRAVEL AND MOTION SICKNESS
by Herman I. Chinn, Ph.D., Chief, Dept. of Pharmacology-Biochemistry, USAF School of Aviation, Randolph Field, Texas.

STRESS AND TRAVEL
by Gaétan Jasmin, M.D., Institute of Experimental Medicine, Montreal, Canada.

SEA TRAVEL AND HEALTH
by William L. Wheeler, Jr., M.D., Medical Director, W. R. Grace & Company, New York City.

GEOGRAPHY, TRAVEL AND DISEASE
by Jacques, M. May Head, Dept. of Medical Geography, American Geographical Society, New York City.

MEDICAL PROBLEMS OF SPACE FLIGHT
by Hubertus Strughold, M.D, Chief, Dept. of Space Medicine, USAF School of Aviation Medicine, Randolph Field, Texas.

PHYSIOLOGIC DAY-NIGHT CYCLE AFTER LONG DISTANCE FLIGHTS
by Hubertus Strughold, M.D., Ph.D., Chief, Dept. of Space Medicine, USAF School of Aviation Medicine, Randolph Field, Texas.

NUTRITION AND FLIGHT
by Col. Miriam E. Perry, Chief, Women's Medical Specialist Corps, USAF, Office of Surgeon General, Washington, D. C.

NEW PERSPECTIVES OF HEALTH AND TRAVEL. A SUMMATION OF THE SYMPOSIUM
by Félix Martí-Ibáñez, M.D., Editor-in-Chief of the INTERNATIONAL RECORD OF MEDICINE & GENERAL PRACTICE CLINICS.

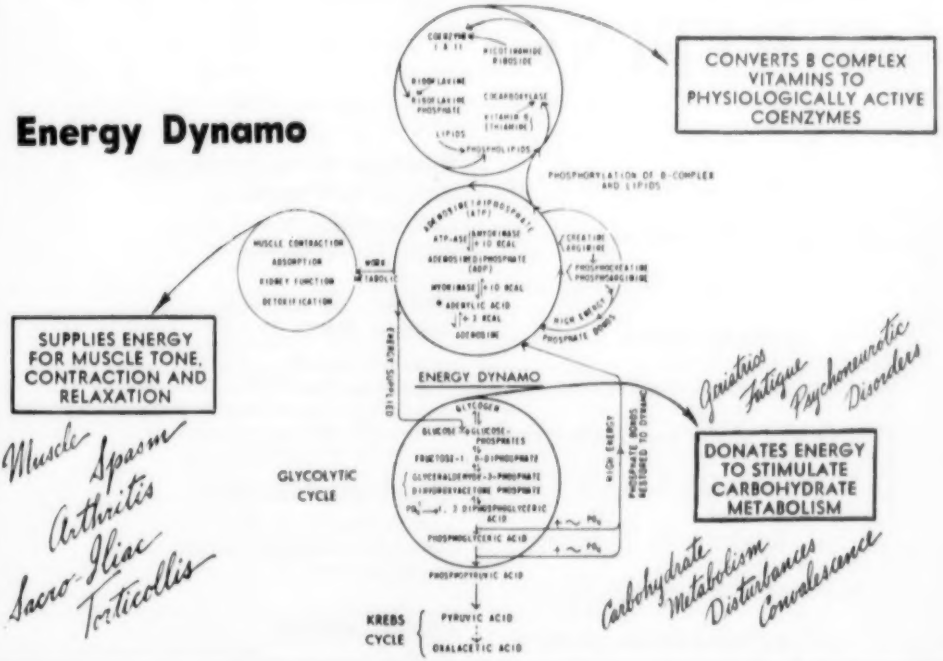
WRITE TO: MD PUBLICATIONS, INC., 30 EAST 60TH STREET, NEW YORK 22, N. Y.

IRONYL®

The Iron Salt of **Adenosine-3-Monophosphate**

THE ROLE OF THE ADENYLIC SYSTEM IN ENERGY EXCHANGES GOVERNING PHYSIOLOGICAL PROCESSES

Energy Dynamo



Clinically

Gradually the role of the Adenylic Nucleotides in clinical medicine is being clarified leading to applications in an expanding number of indications particularly where there are disturbances in the metabolism of muscle energy.

IRONYL is indicated in the treatment of diseases associated with spasm and insufficient relaxation of striated muscles such as arthritis, sacro-iliac, torticollis; in B complex therapy, fatigue and exhaustion.

PHYSIOLOGICAL CHEMICALS COMPANY, Inc.
New Rochelle, N. Y.

PHYSIOLOGICAL CHEMICALS EST. PC 1933

* An annotated Bibliography, "ABSTRACTS ON THE ADENYLIC NUCLEOTIDES" with particular reference to Yeast Adenylic Acid (Adenosine-3-Monophosphate) is available on request.

MD INTERNATIONAL SYMPOSIA MONOGRAPH No. 2

MEDICAL WRITING

Good writing is just as essential in the medical profession as in any other field.

In this symposium, a panel of distinguished medical writers describe the how and why of writing clear and cogent medical articles and books.

Invaluable for the physician interested in the practical principles of medical writing, as well as the enrichment of his own culture in the medical humanities.

A very unusual and attractive book gift for a fellow physician.

72 pp. **Price: $3.00.**

contents

THOUGHTS ON THE PHYSICIAN'S WRITING AND READING
by Henry Sigerist, M.D., Pura, Ticino, Switzerland.

HOW NOT TO WRITE A MEDICAL PAPER
by Hans Selye, M.D., Professor and Director, Institut de Médecine et de Chirurgie Expérimentales, Université de Montréal, Canada.

AN EDITOR'S PREJUDICES
by Hugh Clegg, M.D., Editor, British Medical Journal, *London, England.*

MEDICAL WRITING
by Walter C. Alvarez, M.D., former Professor of Medicine, University of Minnesota; Editor, Modern Medicine, *Chicago, Ill.*

BOOKS IN THE PHYSICIAN'S LIFE
by Félix Martí-Ibáñez, M.D., Editor-in-Chief, International Record of Medicine & General Practice Clinics, *New York City.*

WRITE TO: MD PUBLICATIONS, INC., 30 EAST 60TH STREET, NEW YORK 22, N. Y.

INTERNATIONAL RECORD OF MEDICINE

VOL. 170 NO. 2 WHOLE NUMBER 2888 FEBRUARY 1957

Irving B. Perlstein	The Use of Pipradrol in the Problems of Obesity	55
Milton B. Sloane	Topical and Oral Prednisolone in the Treatment of Dermatoses	59
Mirko Carreras and Franco Angeleri	The Location of Action of Chlorpromazine in the Central Nervous System	67
Albert H. Helm	Value of a Therapeutic Trial with Liothyronine	86
Nandor Fodor	I Dreamed that I Dreamed	92
	MEDICAL INSTRUMENTS SECTION	
H. E. Nieburgs	Modern Cancer Cell Screening Technique	103
	EDITORIAL SURVEY	
	Humpty Dumpty on Writing	108
	BOOK REVIEWS	
William S. Spector, Editor	Handbook of Biological Data	110
Marcus A. Krupp, Normal J. Sweet, Ernest Jawetz, and Charles D. Armstrong	Physician's Handbook, Ninth Edition	110
William G. Sawitz	Medical Parasitology, Second Edition	110
Portia M. Frederick and Carol Towner	The Office Assistant in Medical or Dental Practice	110
Erna Barschak	Today's Industrial Nurse and Her Job	111
George S. Stevenson, Editor	Administrative Medicine, Transactions of the Fourth Conference, October 31, November 1 and 2, 1955, Princeton, N. J.	111
Charles E. Lyght, William P. Boger, George A. Carden, Augustus Gibson, and Dickinson W. Richards, Editors	The Merck Manual, New Ninth Edition	111
Mervin J. Goldman	Principles of Clinical Electrocardiography	112
Milton J. Chatton, Sheldon Margen, and Henry Brainerd, Editors	Handbook of Medical Treatment	112
	INTERNATIONAL CLINICAL NEWSLETTER	opp. p. 112
	ADVANCED REPORTS FROM CURRENT MEDICAL MEETINGS	
	Colloidal Factors in Plasma Gels	113
	Accidental Poisoning in Children	113
	Effects of Hormone Therapy in Aging Patients	114
	Aging in the Atomic Age	114
	Hormone Therapy in Rheumatism	114
	Clinical Observations in Infectious Hepatitis	114
	Development of Measles Vaccine	115
	Variables Affected by Drug Action	115
	Report on BZ-55 and Orinase	116
	Shoulder-Hand Syndrome	116
	Early Treatment Necessary for Orthopedic Conditions	117
	Aspirations of Joints	117
	New Aspects in the Treatment of Amenorrhea and Sterility	117
	Effects of Ataraxics and Asphyxia in Cerebral Palsy	118
	Cholesterol and Diabetes	118

MD INTERNATIONAL SYMPOSIA MONOGRAPH No. 3

Psychiatry *and* Religion

Thirteen scientific authorities and ministers of different religions explore the conflicts of the human psyche and open up new vistas for meaningful cooperation between the psychiatrist and churchman. An absorbing discussion of interest to the psychologist, sociologist, anthropologist, psychiatrist, theologian, religious historian, the clergy, and the intelligent layman. A most unusual and attractively bound volume. 68 pp. **Price: $3.00.**

C O N T E N T S

SYMPOSIUM ON PSYCHIATRY AND RELIGION
An Introduction by Werner Wolff, Ph.D., Professor of Psychology, Bard College, Annandale-on-Hudson, N. Y.

THE PSYCHE AND THE SYMBOLS OF RELIGION
by M. Esther Harding, M.D., M.R.C.P., New York City.

PSYCHOANALYSIS AND RELIGION, AN HISTORICAL VIEW OF FREUD
by Fred H. Blum, Dept. of General Studies, Social Science Program, University of Minnesota, Minneapolis, Minn.

A CURRENT PSYCHOANALYTIC CONCEPT OF GOD
by Josephine H. Ross, Ph.D., New York City.

ANTHROPOLOGIC VIEW OF A PRIMITIVE RELIGION
by Gladys A. Reichard, Professor of Anthropology, Barnard College, Columbia University, New York City.

THE SOCIOLOGIC DEFINITION OF RELIGION
by Joseph Maier, Ph.D., M.A., Newark College of Arts and Sciences, Rutgers University, New Brunswick, N. J.

TOWARDS AN OPERATIONAL DEFINITION OF RELIGION
by Rabbi Samuel Glasner, Ed.D., Director, Dept. of Reform Jewish Education, Board of Jewish Education, Baltimore, Md.

RELIGION AND PSYCHOTHERAPY: PRACTICAL ASPECTS
by Lawson G. Lowrey, M.D., A.M., Asst. Clinical Professor, College of Physicians and Surgeons, Columbia University; Associate in Psychiatry, Vanderbilt Clinic, New York City.

VALUE SYSTEMS IN THE PSYCHOTHERAPEUTIC PROCESS
by Warner L. Lowe, Ph.D., Asst. Director, Alfred Adler Mental Hygiene Clinic, New York City.

PERSONALITY NEEDS, RELIGION, AND PSYCHOTHERAPY
by Alexander A. Schneiders, Ph.D., Professor of Psychology and Director of Psychological Services, Fordham University, New York City.

PSYCHOTHERAPY AND THE MINISTRY
by Abraham N. Franzblau, M.D., Ph.D., Professor of Pastoral Psychiatry and Dean of New York Schools, Hebrew Union College, Jewish Institute of Religion; Asst. Attending Psychiatrist, Mount Sinai Hospital, New York City.

THE NEED TO BELIEVE
by Mortimer Ostow, M.D., New York City.

SPECIAL EDITORIAL:
On Christmas and Neuroses
by Félix Martí-Ibáñez, M.D.

WRITE TO: MD PUBLICATIONS, INC., 30 EAST 60TH STREET, NEW YORK 22, N. Y.

INTERNATIONAL RECORD OF MEDICINE

VOL. 170 NO. 2 WHOLE NUMBER 2888 FEBRUARY 1957

The Use of Pipradrol in the Problems of Obesity

Irving B. Perlstein, M.D.

INSTRUCTOR IN MEDICINE, UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE
LOUISVILLE, KY.

The problem of the obese individual is one that merits the close attention of all who are engaged in the practice of medicine. The deleterious effect of obesity on general health is well illustrated in table I, adapted from longevity data published by the Metropolitan Life Insurance Company.[1]

One successful approach to the obesity problem is presented here. The use of a new drug, pipradrol (Meratran*), as a valuable aid in the treatment of this condition will also be discussed. The technique described in this paper divides the problem into three phases.

Phase 1 begins with the patient's first contact for help with his obesity. An atmosphere of quiet discussion at the very outset gives the patient an opportunity to present his problems related to eating habits, and the physician has an opportunity to establish himself firmly with the patient as an individual sincerely interested in the problem of obesity in general and more specifically in the problems of the particular person. It is important to note that what happens during this first hour of contact with the patient is the key to either future success or failure in treating this problem. In order to ensure a favorable result, the physician must establish himself as a source of strength and support, as someone who has a sound knowledge of the personal problems of the particular patient.

Phase 2 consists of a careful and detailed physical examination with an adequate laboratory work-up. The latter should consist of blood count, urinalysis, erythrocyte sedimentation rate, basal metabolism, blood cholesterol, and a glucose tolerance test including at least the three hour determinations. The metabolism test and blood cholesterol determination will help to rule out thyroid disturbances. The glucose tolerance test is important not only for the detection of diabetes, but also for the detection of functional and organic hypoglycemias, which are frequently the cause of overeating. The first two phases of the program establish for the patient an understanding of the scientific basis for adequate weight control.

* The trade name of The Wm. S. Merrell Co. for pipradrol [α-(2-piperidyl) benzhydrol hydrochloride] is Meratran.

TABLE I

Mortality Rates in 2300 Obese Policyholders

	Lowest extra premium group (least obese)		Higher extra premium group (more obese)	
	Without weight reduction,* per cent	With weight reduction,* per cent	Without weight reduction,* per cent	With weight reduction,* per cent
Men	142	113	179	109
Women	142	90	161	135

* In terms of expected mortality for age group.

Phase 3 is concerned with the problem of compensating for loss of the satisfaction that the overeater derives from his food. Adequate replacement of this satisfaction is essential, since especially during weight reduction the patient is frequently depressed, fatigued, or extremely tense and unhappy. Replacement for the excess food of which the patient is deprived is best provided by his sincere enthusiasm for the weight reduction program and associated with this confidence in his ability to achieve the desired end. Past failures tend to undermine confidence and may produce a serious problem. The sincere interest and enthusiasm of the physician, communicated to the patient as a result of the first two phases, will minimize this difficult problem. Even so, depression and fatigue are still present in many obese persons.

A new drug, pipradrol, has recently been made available as an aid in handling the problems of both adult and juvenile patients with obesity.[2] This agent acts as a central stimulant, elevating the mood, and giving to the patient a feeling of increased self confidence and an enthusiasm for the weight reduction program. In the series of patients here reported, the beneficial effect on mood was remarkable enough to stimulate much comment by their families and others with whom the patients had close contact.

Pipradrol elevated the mood with little or no euphoria. There was no effect on blood pressure, pulse rate, respiration, basal metabolism, urinalysis, or blood count. This absence of side effects has been reported by other investigators.[3–5] It is thought that the role of pipradrol in fostering weight reduction in this series is essentially that of maintaining the patient's elevated happy outlook rather than of acting as an anorexigenic agent. This was well illustrated by several patients who stated that they left the table hungry but were much more confident in their ability to control that hunger after taking pipradrol.

It is interesting to note that two boys, aged 11 and 13 years, who were bed-wetters in addition to being overeaters, stopped bed-wetting when pipradrol therapy was started.

The only undesirable side effect noted from the use of pipradrol was occasional interference with the sleeping habits of some of the patients. Pipradrol was administered in the form of 1.0 mg. tablets (1 or 2 tablets before each meal), and occasionally it was necessary either to eliminate the evening dose of the medication

or to augment it with 60 mg. of phenobarbital, which restored normal sleeping habits.

The elevation of mood that pipradrol produces was noted in many ways. The patients often stated that they had "a new lease on life," that things looked brighter to them, and that they felt like doing many more things than they had previously. They became interested in other things around them, and they increased the scope of their day-to-day and week-to-week activity.

In this group, a total of 35 patients have been treated on a weight reduction regime. The usual weekly weight loss was 2 to 3 pounds. The largest weight loss in one week was 9 pounds. Most of these patients were not on a calorie-counting diet, but rather, on a high protein diet consisting mainly of broiled, baked, or boiled lean meats, skim milk, cheese, and fresh vegetables. They were never restricted in regard to the amount of these foods that they ate. It was found, however, that after one or two weeks of eating all the meat they could get, this diet became slightly unpalatable, and while they adhered to it, the amount of protein they ate became considerably less. In addition it was felt that the contacts with the physician, who emphasized that eating less helped weight reduction, were somewhat responsible for diminished intake. The average person leveled off, eating a diet that contained between 1400 and 1800 calories/day. Each person was weighed once every seven days in the office. It was noted after experimentation with various time intervals that seven days was about the optimum time interval. A period longer than this allowed the patient's interest to wane. At each office visit the patient was allotted 10 to 15 minutes to discuss with the physician the problems that might be bothering him at the moment. This interview actually resembled a miniature psychiatric interview in that the patient was given reassurance, he was urged to continue the progress he was making, and he was, in effect, encouraged by the physician *and the other personnel in the office* with whom he came in contact. It was noted repeatedly that when the office personnel showed enthusiasm and excitement at successful weight loss, the program became much more effective. Eventually it became advisable to instruct the office personnel in this technique, which became a valuable tool.

Gradually, a total personality change became evident in the patients. As they were able to maintain themselves on an adequate dietary program, these people became more confident: they began to approach the scale with confidence and interest rather than with fear and resignation. Pipradrol was discontinued at the completion of the weight loss regime, and no withdrawal symptoms were ever noted.

Pipradrol administered in divided doses during the day is a useful adjunct to the dietary and psychologic treatment of obesity. However, the duration of action is relatively long, and occasionally it is necessary to use phenobarbital at night to overcome a tendency toward insomnia. A single oral dose of 5.0 mg. given before breakfast might be more convenient and might not produce undesirable stimulation late in the day or at night. Accordingly, a series of 37 patients was tried using the single, morning dose of 5.0 mg. of pipradrol instead of the divided doses. The results were the same as those obtained previously and just described, except that insomnia did not occur in any of the patients.

SUMMARY

The approach to the handling of the obese person is multiphasic.

1. The physician must enlarge the patient's confidence both in himself and in the physician.

2. The physician must rule out organic disease by taking a careful history and making complete physical and laboratory examinations.

3. The patient must be made to understand that the problem of each obese person is individual and the success of the weight reduction program depends on the individualization of this program.

4. The physician now has available a new drug, pipradrol, that is an extremely safe and effective aid in maintaining a healthy mental outlook during the monotonous, long weeks of dietary restriction. Pipradrol acts by stimulating the patient's enthusiasm for the weight reduction program rather than by means of an anorexigenic effect. The dosage is 1 or 2 tablets, 1.0 mg. each, before each meal, or a single dose of 5.0 mg. given before breakfast.

BIBLIOGRAPHY

1. Dublin, L. I.: Relation of obesity to longevity, New England J. Med. *248*:971–974, June 4, 1953.
2. Gelvin, E. P.; McGavack, T. H., and Keniosberg, S.: α-(2-Piperidyl) benzhydrol hydrochloride (pipradrol) as an adjunct in the dietary management of obesity, New York State J. Med. *55*:2336–2338, Aug. 15, 1955.
3. Fabing, H. D.: Clinical experience with Meratran, Dis. Nerv. System *16*:3–8, Jan., 1955.
4. Brown, B. B., and Werner, H. W.: Pharmacologic studies on a new central stimulant, α-(2-piperidyl) benzhydrol hydrochloride (MRD-108), J. Pharmacol. & Exper. Therap. *110*:180–187, Feb., 1954.
5. Antos, R. J.: A preliminary report of clinical studies on a new stimulant, Arizona Med. *11*:307–309, Nov., 1954.

Ars Medica

Eighty-five prints representing the teaching and practice of medicine were exhibited during the month of October at the New York Academy of Medicine. The collection is entitled *Ars Medica*, or the Healing Arts, and is owned by the Philadelphia Museum of Art.

The prints, assembled into 15 panels depicting the various phases of medical history and practice, were included in the collection for both their artistic quality and their medicohistorical value. Artists and illustrators, such as Bruegel, Daumier, Goya, Hogarth, Holbein, Kollwitz, Lautrec, Rembrandt, Steen, and Wechtlin, are represented; some of the prints are well known, others are rare.

Topical and Oral Prednisolone in the Treatment of Dermatoses

Milton B. Sloane, M.D.

ENGLEWOOD, N. J.

After the development of prednisone and prednisolone, these steroids were soon tried in dermatology because of their resemblance to older corticosteroids. Used first orally, they proved to be effective in various disorders of the skin.[1–18]

Some of the first ointments and creams containing prednisolone were made available to me for clinical evaluation. Prednisone is ineffective, or less consistently effective, than prednisolone when applied to the skin.[7, 14] Goldman et al[7] demonstrated that both prednisone and prednisolone possess anti-inflammatory activity on intracutaneous injection. By their assay techniques, prednisolone was the more active.

Whereas the skin in approximately one third of patients was irritated by the first experimental prednisolone ointments tried,[14] little irritation has occurred in recent studies in patients treated with 0.5 per cent prednisolone ointment now available.[19, 20] Goldman et al[7] encountered no irritation among 145 patients treated with prednisolone ointments and lotions of 0.1 to 0.5 per cent strength. In my experience with several series of patients, the incidence of irritation has been low with the topical preparations of prednisolone used recently.

Early in my studies, the effectiveness on topical application in dermatologic conditions of prednisolone alcohol was compared with that of prednisolone acetate. Similar to the experience of Sulzberger and Witten[21, 22] with hydrocortisone alcohol and hydrocortisone acetate topically, prednisolone alcohol 0.5 per cent proved to be somewhat more effective than prednisolone acetate 0.5 per cent in a similar base. It produced better results in a higher percentage of patients. Both preparations were as effective as 0.5 per cent hydrocortisone alcohol, prednisolone alcohol 0.5 per cent possessing some advantage.

TOPICAL ADMINISTRATION

Prednisolone Cream. After the preliminary studies, prednisolone alcohol 0.5 per cent in a cream type base* was tested in 45 patients with the dermatoses listed in table I. The patients were instructed to apply a thin coating of the cream to affected areas three times daily. The duration of administration varied from one to three weeks.

The response to prednisolone cream was usually rapid and became apparent within one or two days. The relief of pruritus was a consistent effect. Erythema lessened and the lesions began to flatten and regress.

Dermatitis venenata, *neurodermatitis*, *pruritus ani and vulvae*, *atopic dermatitis*, and *nummular eczema* responded well in most cases. A single patient with *varicose eczema*

* The trade name of Schering Corp. for prednisolone is Meti-Derm.

TABLE I

Results with Prednisolone Cream

Diagnosis	No. pt.	Cured	Improved	Unchanged	Irritated
Dermatitis venenata	16	6	6	2	2
Dermatitis, atopic	9	1	6	2	—
Eczema, nummular	2	1	1	—	—
Eczema, varicose	1	—	1	—	—
Lichen planus	1	—	—	1	—
Neurodermatitis	9	3	6	—	—
Pityriasis rosea	1	—	—	1	—
Pruritus ani	4	2	2	—	—
Pruritus vulvae	2	—	2	—	—
Total	45	13	24	6	2
Per cent		29.0	53.3	13.3	4.4

was moderately improved. The lesions disappeared from 13 patients in the series. There were various degrees of improvement in 24 patients. In a few of these, the conditions relapsed despite continued application of the cream.

A treatment failure occurred in 1 patient with *pityriasis rosea* and in 1 with *lichen planus*. The cream had to be discontinued because the skin of 2 patients with dermatitis venenata was irritated.

The over-all results led to the conclusion that prednisolone cream is highly effective in dermatoses responsive to corticosteroids applied locally.

Prednisolone with Neomycin Ointment.[23, 24] The finding that steroid ointments, in the presence of infection, may not only produce no improvement in, but actually aggravate, a skin eruption suggested the combination of an antibacterial agent with prednisolone for topical application. The combination of these substances was indicated also for dermatoses with secondary pyogenic infection inasmuch as prednisolone does not curtail the growth of microorganisms.

An ointment containing 0.5 per cent prednisolone alcohol with 0.5 per cent neomycin sulfate in a petrolatum base was tested in 140 patients with the conditions listed in table II. Many of these patients had been treated with other substances locally with variable and often unsatisfactory results. The directions for use of the ointment were the same as for prednisolone cream: that is, three applications per day sparingly over affected areas.

The response to prednisolone ointment with neomycin also occurred rapidly, usually within a day or two. Pruritus was usually promptly relieved and lesions began to fade. Infection when present subsided. The duration of therapy was from one to two weeks in the acute dermatoses and those with secondary infection. Treatment was carried out for three to five weeks in some cases of atopic dermatitis, nummular eczema, neurodermatitis, dermatitis venenata, infectious eczematoid dermatitis, and dermatitis venenata with secondary infection.

The results of therapy are given in table II. Responsive dermatoses included *dermatitis venenata*, *atopic dermatitis*, *nummular eczema*, and *neurodermatitis alone and*

complicated by dermatitis venenata or pruritus ani and vulvae. One patient each with the following diseases was cured or markedly improved: *varicose eczema with secondary eczematization*, *varicose eczema complicated by dermatitis venenata*, *neurodermatitis complicated by dyshidrosis*, and *varicose ulcer*.

Infectious eczematoid dermatitis and *secondarily infected seborrheic dermatitis* also showed a good response to the topical antibiotic-steroid combination. Single cases of *pustular bacterid* and *atopic dermatitis with secondary infection* were cured. The results in *dermatitis venenata with secondary infection* varied—in 2 patients the lesions remained unchanged whereas in 3 others they regressed noticeably and the infection cleared.

Only 1 of 2 patients with *varicose eczema* derived any benefit from the ointment. Itching ceased in a patient with *eczematized psoriasis and neurodermatitis* but residual psoriatic scaling remained. The improvement was probably due to the disappearance of the localized neurodermatitis. This patient was switched to antipsoriatic therapy. The marked improvement in 1 patient with *eczematized psoriasis* and temporary improvement in another were due to the lessening of irritation. No attempt was made to treat the psoriasis. *Irritation in uncomplicated psoriasis* was relieved in 1 patient but unaltered in a second.

A patient with *varicose eczema secondarily infected* and 1 with *lichen planus complicated by dermatitis venenata* showed only temporary improvement. The eruptions recurred despite the continued application of the ointment.

A good result was obtained in a patient with *Rhus dermatitis* in whom the eruption was subsiding following the use of calamine lotion. However, prednisolone cream and prednisolone ointment with neomycin usually proved of little value in this condition and accomplished only slight alleviation of itching. Prednisone and prednisolone administered orally are of benefit in *Rhus* dermatitis. In general, it was found that vesicular and bullous eruptions did not respond to the local application of prednisolone.

Herpes simplex, *discoid lupus erythematosus*, the cutaneous manifestations of *subacute lupus erythematosus*, *otitis externa complicated by infectious eczematoid dermatitis*, and *pityriasis rosea* failed to respond. Symptoms in the patient with subacute lupus erythematosus were relieved but no change occurred in the patient's appearance. Prednisone was administered orally to control the systemic disease.

All lesions disappeared during therapy from a total of 31 patients. Marked improvement occurred in 55, so that a major degree of benefit was afforded in 86, or 61.4 per cent, of the patients in the series. Many of those markedly improved at the time of evaluation of therapy were later able to discontinue application of the ointment. The improvement was only temporary in 18 patients and the condition recurred despite continuation of the ointment. Twenty-nine patients, 20.7 per cent, failed to respond.

Untoward reactions occurred in 9 patients and caused the discontinuation of local therapy in 7 of them (5 per cent). The ointment was continued despite moderate burning on application in 1 patient with nummular eczema who had a good response. The maceration of perirectal tissues forced its discontinuation at this site in a case of neurodermatitis complicated by pruritus ani and vulvae, but the ointment could be continued on other areas. The causes for discontinuation and

TABLE II

Results with Prednisolone with Neomycin Ointment

Diagnosis	No. pt.	Cured	Marked improvement	Temporary improvement	Unchanged	Untoward reactions
Bacterid, pustular	1	1	—	—	—	—
Dermatitis, atopic	28	2	12	8	3	1 itching accentuated 2 irritation
Dermatitis, atopic with secondary infection	1	1	—	—	—	—
Dermatitis, infectious eczematoid	7	2	3	—	1	1 irritation
Dermatitis, *Rhus*	1	1	—	—	—	—
Dermatitis, seborrheic, with secondary infection	2	1	1	—	—	—
Dermatitis venenata	24	8	9	3	3	1 irritation, burning
Dermatitis venenata with secondary infection	5	—	3	—	2	—
Eczema, nummular	14	5	7	1	1	1 moderate burning on application*
Eczema, varicose	2	—	1	—	1	—
Eczema, varicose, with secondary eczematization	1	—	1	—	—	—
Eczema, varicose, with secondary infection	1	—	—	1	—	—
Eczema, varicose; dermatitis venenata	1	1	—	—	—	—
Herpes simplex	7	1	—	—	6	—
Lichen planus; dermatitis venenata	1	—	—	1	—	—
Lupus erythematosus, discoid	3	—	—	—	3	—
Lupus erythematosus, subacute	1	—	—	—	1	—
Neurodermatitis	21	6	10	1	3	1 burning on application
Neurodermatitis; dermatitis venenata	3	1	2	—	—	—
Neurodermatitis; dyshydrosis	1	—	1	—	—	—
Neurodermatitis; pruritis ani and vulvae	2	1	1	—	—	1 maceration of perirectal tissues†
Otitis externa; dermatitis, infectious eczematoid	1	—	—	—	1	—
Pityriasis rosea	1	—	—	—	1	—
Psoriasis, eczematized	2	—	1	1	—	—
Psoriasis, irritated	2	—	1	—	1	—
Psoriasis, eczematized; neurodermatitis	1	—	1	—	—	—
Psoriasis, pustular	4	—	—	2	2	—
Ulcer, varicose	1	—	1	—	—	—
Ulcer, varicose, with secondary eczematization	1	—	—	—	—	1 hypersensitivity reaction
Total	140	31	55	18	29	7
Per cent		22.1	39.3	12.8	20.7	5.0

* Ointment continued. † Ointment continued on other areas.

the numbers of patients affected were: burning on application, 1; accentuation of itching, 1; hypersensitivity reaction, 1; and irritation, 4. The patient with a sensitivity reaction was also hypersensitive to all greases and had an exacerbation of a varicose ulcer with secondary eczematization after 25 days of therapy.

Some outstanding responses occurred in patients who had not benefited, or who had improved only temporarily, with other kinds of therapy. For example, in one 28 year old woman with atopic dermatitis, in whom the eyelids and popliteal areas showed extensive erythema and scaling, oral prednisone brought about temporary improvement but hydrocortisone ointment locally was ineffective. Prednisolone ointment with neomycin produced marked improvement in this patient and was the only local application of benefit. Another patient with secondarily infected atopic eczema, who improved under roentgen-ray and topical iodochlorhydroxyquin and α-fluorohydrocortisone therapy, showed a remarkable change and was cured through the use of prednisolone ointment with neomycin. A patient with a prolonged history of neurodermatitis, complicated recently by dermatitis venenata, improved temporarily when treated with ultraviolet rays, vitamin A, and a "shake" lotion, but an exacerbation occurred while these were being continued. Both diseases were brought under control and the lesions disappeared when prednisolone ointment with neomycin was applied for a few weeks.

SYSTEMIC ADMINISTRATION

Oral Prednisone and Prednisolone. Prednisone or prednisolone was given orally to 144 patients for the treatment of the dermatoses listed in table III. The plan for dosage was to start with relatively large amounts, that is, 40 to 60 mg. the first day, to decrease to 30 mg. the second and third days, and then to reduce the dosage progressively in accordance with the response of the condition and the severity of the symptoms. The initial dosage in pemphigus vulgaris was 120 mg./day.

No attempt was made to compare the response to prednisone with that to prednisolone. Both steroids appeared to be equally effective orally and could be interchanged at will.

The acute dermatoses and herpes zoster were treated on an average for 5 to 10 days. Steroid therapy in chronic urticaria was evaluated after one week and in pemphigus vulgaris and disseminated lupus erythematosus after two weeks to one month. Patients with chronic urticaria were treated for 5 to 10 days. The disease showed a tendency to recur after the cessation of treatment but the recurrences were usually relatively mild.

Rhus dermatitis was readily controlled by oral prednisone therapy. Both the pruritus and the lesions disappeared rapidly in the majority of 75 patients. Four patients were unimproved. *Lichen planus* and *pityriasis rosea*, which also had been unresponsive to the local application of prednisolone, showed marked or moderate improvement in all patients. Two patients with the former relapsed when prednisone was discontinued. The other responsive conditions were: *exfoliative dermatitis, dermatitis venenata, nummular eczema, erythema multiforme, subacute lupus erythematosus, disseminated neurodermatitis, pemphigus vulgaris, pruritus gestationis*, and *acute and*

TABLE III

Results with Oral Prednisone and Prednisolone

Diagnosis	No. pt.	Marked improvement	Moderate improvement	Unimproved	Untoward reactions
Dermatitis, exfoliative	3	2	1	—	—
Dermatitis venenata	8	8	—	—	—
Eczema, nummular	3	2	—	1	—
Erythema multiforme	3	2	1	—	—
Herpes zoster	13	10	2	1	—
Lichen planus	4	2	2	—	—
Lupus erythematosus, subacute	2	2	—	—	—
Neurodermatitis, disseminated	12	6	3	1	1 excitation 1 gastric upset
Pemphigus vulgaris	2	2	—	—	—
Pityriasis rosea	5	4	1	—	—
Pruritus gestationis	3	3	—	—	—
Rhus dermatitis	75	65	3	4	2 excitation 1 gastric upset
Sarcoid, Boeck's	2	—	—	2	—
Urticaria, acute	6	6	—	—	—
Urticaria, chronic	3	3	—	—	—
Total	144	117	13	9	5
Per cent		81.3	9.0	6.3	3.4

chronic urticaria. Among 13 patients with *herpes zoster*, 10 were markedly and 2 moderately improved. In 1 patient in each group, the eruption cleared rapidly but neuritic pain persisted. Symptomatic improvement occurred in 1 additional patient with herpes zoster but the clinical course of the disease remained unchanged. Therapy has been temporarily discontinued in 1 of the patients with pemphigus vulgaris. The second patient is being maintained on a daily dosage of 15 to 20 mg.

Three women with pruritus gestationis and a fourth pregnant patient with dermatitis venenata had no untoward effects from prednisone or prednisolone therapy.

The oral steroids had to be discontinued in 3 patients because of mental excitation and in 2 because of a gastric upset after administration for three days. The former patients could not sleep or rest. The latter complained of upper abdominal pain and nausea on the second day. The distress disappeared immediately on discontinuation of the steroid. Antacids were not given. A patient with pemphigus, receiving up to 200 mg./day of prednisone, showed transient glycosuria that was controlled by the administration of insulin. In no patient was there evidence of fluid retention, gastric hemorrhage, or cardiovascular damage.

SUMMARY

By topical application, prednisolone free alcohol is more effective than prednisolone acetate. In a cream type base, prednisolone is equally as or more effective than hydrocortisone or α-fluorohydrocortisone in a similar base. Tested in 45 patients

with various dermatoses, 0.5 per cent prednisolone cream controlled the condition or brought about significant improvement in *dermatitis venenata*, *neurodermatitis*, *pruritus ani and vulvae*, *atopic dermatitis*, and *nummular eczema*. Lichen planus and pityriasis rosea were not controlled. An ointment containing prednisolone 0.5 per cent and neomycin sulfate 0.5 per cent tested in 140 patients satisfactorily controlled a variety of dermatologic conditions some of which were complicated by secondary infection. Cutaneous infections like *pustular bacterid* and *infectious eczematoid dermatitis* were cleared. Few untoward effects accompanied the use of prednisolone cream and ointment. The skin was irritated by the cream in 2 patients and by the ointment in 4 patients.

Among conditions treated with the steroids orally, an excellent response was obtained in *exfoliative dermatitis*, *dermatitis venenata*, *nummular eczema*, *erythema multiforme*, *subacute lupus erythematosus*, *disseminated neurodermatitis*, *pemphigus vulgaris*, *pruritus gestationis*, *acute and chronic urticaria*, and *herpes zoster*. No untoward effects were noted in 4 pregnant patients receiving the steroids orally. The only side effects following the steroids orally were excitation in 3 patients, transient glycosuria in 1 patient, and in 2 patients gastric upset that subsided when the steroid was discontinued.

ACKNOWLEDGMENT

The prednisolone cream and prednisolone with neomycin ointment used in this study were furnished by G. Kenneth Hawkins, M.D., Division of Clinical Research, Schering Corp., Bloomfield, N. J.

BIBLIOGRAPHY

1. Alcantara Madeira, J.: Prednisolone, prednisone "remarkable" in dermatoses, Hospital, Rio de Janeiro *49*:209 (Feb.) 1956; abstr., Hormone Newsletter (May) 1956.
2. Andrews, G. C., and Domonkos, A. N.: Clinical results of treatment with metacortandracin in discases of the skin. Preliminary report, First International Conference, Meticorten, New York, May 30–June 1, 1955.
3. Brown, E. A., and Clancy, R. E.: Comparative studies of the efficacy of Meticorten and cortisone in allergic disorders, First International Conference, Meticorten, New York, May 30-June 1, 1955.
4. Caccialanza, P.: Terapia del pemfigo e di altre dermatosi mediante somministrazione di un nuovo steroide cortisonosimile: il prednisone, Minerva med. *46*:1741–1744 (Dec. 12) 1955.
5. Dillaha, C. J.: Bullous dermatitis herpetiformis, J. Arkansas M. Soc. *52*:255–257 (April) 1956.
6. Frank, L., and Stritzler, C.: Prednisolone topically and systemically. A clinical evaluation in selected dermatoses: preliminary report, A. M. A. Arch. Dermat. & Syph. *72*:547–549 (Dec.) 1955.
7. Goldman, L.; Flatt, R., and Baskett, J.: Preliminary and short report. Assay technics for local anti-inflammatory activity in the skin of man with prednisone and prednisolone, J. Invest. Dermat. *25*:75–76 (Aug.) 1955.
8. Hansel, F. K.: Medical otolaryngology, Laryngoscope *66*:449–464 (April) 1956.
9. Midana, A., and Zina, G.: Prime osservazioni sull'impiego del prednisone in campo dermatologico, Minerva med. *46*:5–8 (July 5) 1955.
10. Montilla, G., and Pisani, M.: Prime esperienze terapeutiche con il prednisone in dermatologia, Ann. Italiani dermat. e sif. *10*:4 pp. (Sept.-Dec.) 1955.
11. Nelson, C. T.: Preliminary and short report. Pemphigus vulgaris treated with metacortandracin. Case report, J. Invest. Dermat. *24*:377–378 (April) 1955.
12. Nelson, C. T.: Prednisone (Meticorten) in the treatment of pemphigus. A preliminary report, First International Conference, Meticorten, New York, May 30-June 1, 1955.

13. Rein, C. R., and Bodian, E. L.: A clinical evaluation of prednisone in the treatment of dermatoses, First International Conference, Meticorten, New York, May 30-June 1, 1955; A. M. A. Arch. Dermat. & Syph. *73*:378–381 (April) 1956.
14. Robinson, H. M., Jr.: Prednisone and prednisolone in the treatment of dermatoses, First International Conference, Meticorten, New York, May 30-June 1, 1955.
15. Robinson, H. M., Jr.: Prednisone in treatment of selected dermatoses. Preliminary report, J. A. M. A. *158*:473–475 (June 11) 1955.
16. Rose, B., and MacKenzie, K. R.: Preliminary metabolic and clinical observations on the use of Meticorten (prednisone) in cases of allergy, First International Conference, Meticorten, New York, May 30–June 1, 1955.
17. Sidi, E.: Prednisone in allergic dermatoses, Meeting, Pediatric Society, France, abstr., J. A. M. A. *161*:260 (May 19) 1956.
18. Tanca Marengo, J.: Meticorten en artritis reumatoide, psoriasis, asma y otras afecciones alergicas y del sistema colageno, Soc. Medico-Quirurgica del Guayas, July 6, 1955; Gac. méd. *10*:495–504 (July-Aug.) 1955.
19. Robinson, R. C. V., and Robinson, H. M.: Topical treatment of dermatoses with steroids, South. M. J. *49*:260–266 (March) 1956.
20. Robinson, H. M., Jr.; Robinson, R. C. V.; Strahan, J. F., and Cohen, M. M.: Steroid preparations for topical therapy of skin eruptions. Read before the Panel on Military Medicine, American Academy of Dermatology & Syphilology, Chicago, December, 1955. In press.
21. Sulzberger, M. B., and Witten, V. H.: Hydrocortisone (compound F) free alcohol ointment. Letter to the editor, J. A. M. A. *152*:1456 (Aug. 8) 1953.
22. Sulzberger, M. B., and Witten, V. H.: Hydrocortisone ointment in dermatologic therapy, M. Clin. North America *38*:321–336 (March) 1954.
23. Robinson, H. M., Jr.; Robinson, R. C. V., and Strahan, J. F.: Antibiotic-steroid combinations for topical use. *In:* Antibiotics Annual 1955–1956, New York, Medical Encyclopedia, Inc., 1956, pp. 302–306.
24. Noojin, R. O.: The dermatologic management of pruritis, South. M. J. *49*:149–155 (Feb.) 1956.

MD Publications to Present Exhibit at Meeting of American College of Physicians

MD Publications, Inc., will be represented with a technical display at the Thirty-eighth Annual Session of the American College of Physicians, which will be held in Boston from April 8 to 12. The 1957 display booth of MD Publications will feature (1) MD, the new medical newsmagazine; (2) the six other journals of MD Publications: Antibiotics & Chemotherapy, Antibiotic Medicine & Clinical Therapy, International Record of Medicine, Quarterly Review of Pediatrics, Journal of Clinical and Experimental Psychopathology & Quarterly Review of Psychiatry and Neurology, and Quarterly Review of Surgery, Obstetrics and Gynecology; and (3) *Antibiotics Annual 1956-1957*, containing 155 reports on the latest findings in antibiotics by 390 authors representing 12 countries.

Other books published recently by MD Publications, Inc., will also be exhibited. These include: the MD International Symposia Monographs—*Health and Travel*, *Medical Writing*, *Psychiatry and Religion*, and *Medicine and Writing*.

The Location of Action of Chlorpromazine in the Central Nervous System

Mirko Carreras and Franco Angeleri

NERVOUS AND MENTAL DISEASES CLINIC, UNIVERSITY OF PARMA

PARMA, ITALY

As is known from recent studies, the behavior patterns as well as the electrocortical reactions typical of the waking state and of sleep depend on functional changes of a neuronal system that is present in the reticular formation of the cerebral stem and that consists of a complex series of ascending pathways leading to the basal diencephalon. The interplay seems to constitute, in the light of recent knowledge, the physiologic basis of sensation and perception.

In line with such important neurophysiologic assumptions, a whole series of experiments has been instituted aimed at clarifying the location of action in the central nervous system of certain substances, some of them in current use in the practice of neuropsychiatry and anesthesiology.

The experiments conducted to date have proved that those complex subcortical mechanisms that constitute the ascending reticular system are particularly sensitive to the action of stimulating or depressant drugs as well as to metabolic changes.

In recent years attention has been directed from many sides to the study of a substance chemically close to the amino-derivatives of phenothiazine; namely, chlorpromazine, which is endowed with interesting pharmacodynamic properties.

In addition to sympathicolytic, antispasmodic, and hypothermic effects, it has been recognized that chlorpromazine has the property of potentiating the action of sedatives and hypnotics.

This drug, however, has proved able by itself to induce in human and animal subjects a state of sedation and light sleep, thus making obvious its important action on the central nervous system.

The interest aroused by chlorpromazine has given impulse to a series of research studies aimed at investigating the mechanism and the location of action of the drug. The experiments reported in the present paper deal with this subject.

MATERIALS AND METHODS

The experiment was conducted on waking cats immobilized by curare, administered intravenously in such dosage as not to modify electric activity of the brain, or on *encéphale isolé* preparations.

The operation on the skull was performed with quick-acting ether anesthesia of short duration. It consisted in opening the cranial vault, symmetrically screwing into it some screw electrodes at different points of the neopallium for the electroencephalographic re-

© Copyright 1956 by MD Publications, Inc. All rights reserved.

cording, and making one or more openings in the bone for the exposure of a cortical area or to permit the insertion of subcortical coaxial electrodes.

The correct placing of the latter was ensured by a stereotactic instrument.

The cortical recording was made—by means of a one-directional conductor derived from the main conductor—with an electrode formed by a thin tuft of cotton impregnated with physiologic solution, supported by a small spring of silver chloride set on the lid of a small cylinder to be inserted into the bone hole made to fit.

The acoustic stimulation was effected by a signal obtained by an electric impulse inserted into a circuit of a dynamic diffusor; in other cases, sensory stimulation was elicited by means of single electric shocks applied to the sciatic nerve. It was thus possible to record potentials brought about in the reticular formation of the mesencephalon and in the respective cortical areas of specific projection.

For the direct stimulation of the reticular formation of the encephalic stem, an electronic apparatus was used generating rectangular impulses of varied duration, frequency, and voltage. Indirectly an electroencephalogram was obtained of the reactions during the waking state by means of painful or frequently repeated sensory stimuli.*

The drugs were administered either intravenously or locally.

The study of cortical activity was carried one step further by oscillographic means, using a cathode tube, by means of single photograms of the primary cortical reactions and of the hypersynchronous activity induced by the drugs.

CHANGES OF THE ELECTROENCEPHALOGRAM INDUCED BY CHLORPROMAZINE IN HUMAN BEINGS AND IN ANIMALS

The study of the encephalographic changes following administration of chlorpromazine was conducted in human subjects and in animals. In the cat such a study was made by means of the *encéphale isolé* preparation—or in the waking state after immobilization with curare. In the human subject the electrographic recording was set on some time after the drug had been given intramuscularly in a dosage that varied from 50 to 100 mg. The recording proceeded uninterruptedly in order to check the various phases prior to the onset of sleep. The study was finally completed by a comparison of the encephalograms of the human and animal subjects while under the influence of barbiturate narcosis.

The most striking effect following the intravenous administration of chlorpromazine in dosages of 3 to 5 mg./Kg. is represented by the setting in of a sleeping state from which the animal can easily be awakened by means of acoustic and painful stimuli. The awakening is prompt, and its duration depends on the intensity and nature of the stimulus; in general, the waking state lasts longer if the stimulation has been painful. Parallel to the subsidence of the waking state, profound changes in the electroencephalogram appear. Following the rapid activity of the waking state, slow rhythms of increasing voltage progressively set in, among which are interspersed the characteristic spindle bursts that are at first sporadic and afterward more frequent and regular, particularly in the anterior areas (fig. 1).

* For the electroencephalographic and electrocorticographic recording, the electroencephalograph REEGA X was used.

The transition of the diagram from the waking state to that of sleep occurs gradually if the administration of the drug is slow. In contrast, the quick introduction of the same dosage causes a rapid fall of the pressure as well as a marked reduction of the cortical electrogenesis, which may reach the point of electric silence lasting in general not more than 60 to 90 seconds. The electric silence is followed by a gradual reinstatement of the cortical rhythms with the normal characteristics of the state of sleep together with the partial return of the pressure values.

From what has been stated above, it seems clear that the electrographic picture of the state of sleep induced by chlorpromazine does not differ from that of spontaneous sleep. However, there is a difference in the sensory stimuli produced in the animal subjected to chlorpromazine; namely, an electrocortical reaction of shorter duration in the waking state.

Similar changes of the electric activity of the brain are recorded in the waking human subject injected with chlorpromazine. In the human being, the electroencephalogram during sleep passes through successive phases characterized by progressive regularization and increase of the amplitude of the alpha rhythm followed by a slowing down of the fundamental frequency and reduction of the average voltage. This gradual transition is observed more frequently in individuals with a basic desynchronized electroencephalogram.

Figure 2 shows the electroencephalogram recording the reactions of a subject affected by anxiety syndrome before and after subcutaneous administration of 50 mg. of chlorproma-

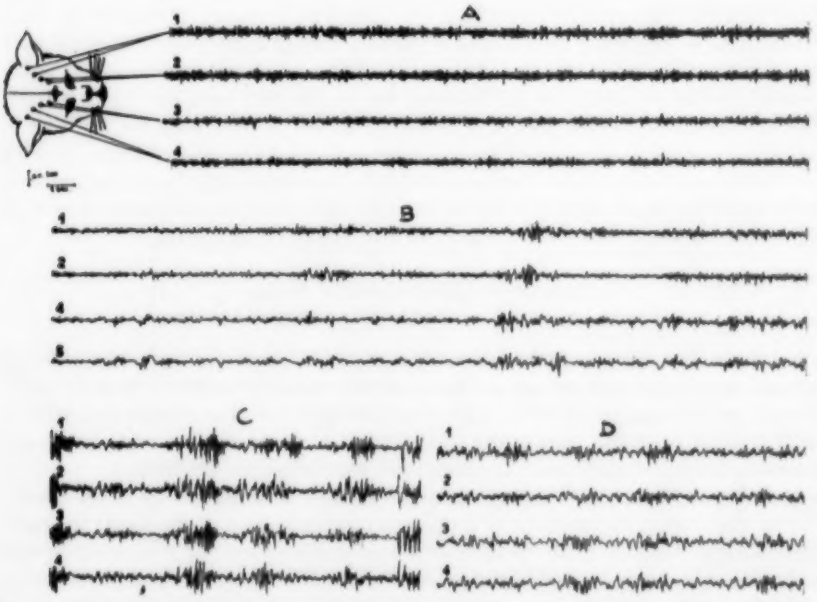


FIG. 1. Electroencephalogram of cat in waking state under the influence of curare (A). B, C, and D: Changes induced by intravenous administration of 2 mg./Kg. of chlorpromazine after 30 seconds, three minutes, and five minutes, respectively.

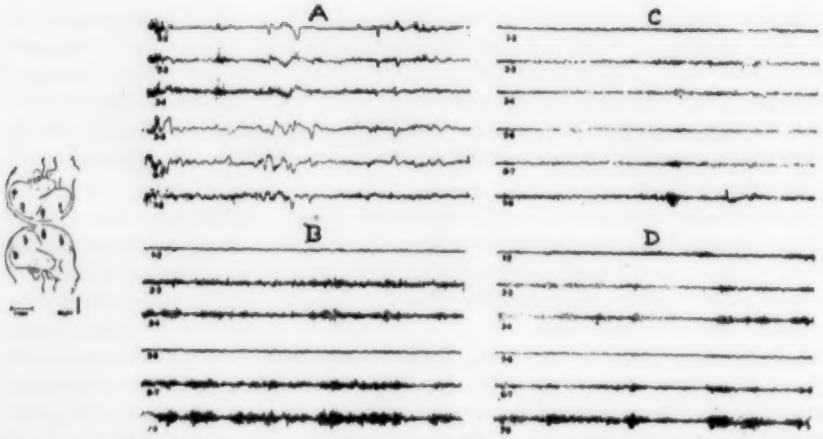


FIG. 2. A: Electroencephalogram of an adult woman in a state of anxiety. B, C, and D: Electroencephalograms of the same subject after intramuscular administration of 25 mg./Kg. of chlorpromazine after 10, 15, and 20 minutes, respectively.

zine. One can observe the progressive regularization of the electroencephalogram, which before treatment appeared desynchronized and altered by artifacts. In figure 3 the electroencephalogram recording the reactions of the same subject during sleep 45 minutes after the injection is compared with the electroencephalogram during sleep induced by barbiturates. Besides the absence in the former of the characteristic rapid activity of the first phase of barbiturate-induced sleep, it is interesting to note in the 2 cases the difference in the cortical reaction to sensory stimulation. Whereas the reaction of the subject on awaking from barbiturate-induced sleep is expressed in the electroencephalogram by the reappearance of the above-mentioned rapid activity, in the sleep induced by chlorpromazine the return of the alpha rhythm is analogous to that which occurs in physiologic sleep.

EFFECTS OF CHLORPROMAZINE ON THE CORTICAL REACTIONS PRODUCED BY SENSORY STIMULATION

It is known that the primary cortical reaction of sensory projection to a stimulus carried through the afferent pathways is composed of two elements: first, the properly called primary reaction constituted by a variation of potential that in monopolar derivation is positive in the beginning; second, the afterdischarge or protracted rhythmic reaction expressed by a series of oscillations of potential that prolong the primary reaction.

According to Bremer,[8] one has to distinguish two aspects of the sensory afterdischarge, each of them being characteristic of a different functional state of the brain: the rapid afterdischarge observed in the nonnarcotized waking animal and the slow afterdischarge observed in the states of functional depression of the brain (narcosis, spontaneous sleep, etc.). The first aspect represents, according to Bremer, a rapidly passing intensification of the cortical activity and is similarly reinforced by corticipetal influences of thalamic origin.

The second reflects the reaction of the interneurons of the cortical projection area to the

impulses originating rhythmically in the nuclei of thalamic relay, whose tendency to an autochthonous synchronized rhythm is more resistant than that of the cortical neurons to depressive states. In other words, Bremer considers that the slow afterdischarge represents the effect on the depressed cortex exerted by the rhythmic activity of the thalamic nuclei of sensory relay.

Chlorpromazine injected intravenously in dosages of 3 to 10 mg. into the nonnarcotized and awake animal affects the cortical reaction to sensory stimuli, but the changes induced by the drug do not concern the primary reaction but rather the afterdischarge.

In fact, while the positive and negative components of the produced primary potential retain their characteristic amplitude and shape unaltered, prolonged rhythmic reaction of the cortex slows down considerably, assuming the appearance of the slow afterdischarge (fig. 4).

Greater doses (10 to 15 mg./Kg.) cause the disappearance of the afterdischarge, while the primary reaction still remains unchanged, as can easily be observed in the oscillographic recording.

From what has been said so far, it has been shown that chlorpromazine in the dosages used neither modifies the conduction of the impulses along the primary afferent systems nor obstructs the transcortical activation of the neurons, which are responsible for the corticofugal discharge as expressed by the negative component of the primary reaction. Equally negative is the effect of the drug in varied concentrations applied directly to the cortex.

The changes of the sensory afterdischarge following the administration of chlorpromazine are imputable, according to our point of view, to a depression of cortical tone determined not so much by direct action of the drug on the cellular systems of the cortex as rather by the dwindling of the control activating the cortical tone arising from the ascending reticular system, the functional state of which is directly influenced by the drug, as we shall describe later.

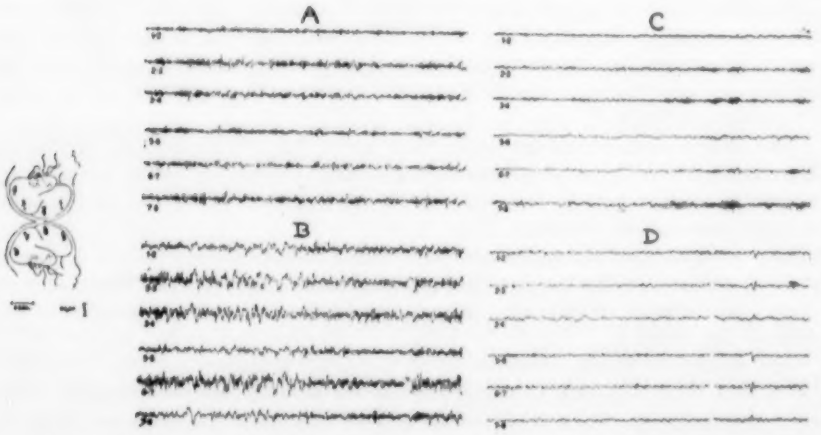


FIG. 3. Comparison between the electroencephalogram of the first phases of sleep induced by barbiturates (A and B) and that of sleep induced by chlorpromazine (C and D).

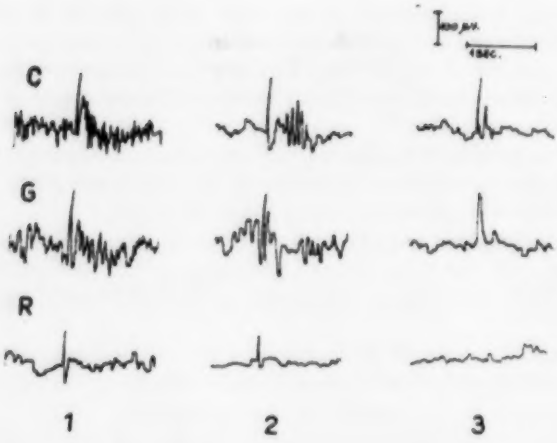


FIG. 4. Effects of chlorpromazine on the activity evoked in the primary acoustic area (C), in the medial geniculate ganglion (G), and in the reticular substance of the mesencephalon (R) due to an acoustic stimulus in the *encéphale isolé* cat. (1) Before administration, (2) during the slow intravenous injection of 3 mg./Kg. of chlorpromazine, and (3) four minutes after injection of same.

INFLUENCE OF CHLORPROMAZINE ON THE EXCITABILITY OF THE RETICULAR FORMATION OF THE BRAIN STEM

The studies of Allen[1] and of Berry et al[7] have proved that collateral fibers directed to medial areas of the brain stem and the diencephalon arise from the sensitive and sensory projection pathways. The successive studies of Moruzzi and Magoun[28] have proved that in these areas are located complex mechanisms to which are attributed ascending influences on the cortex that account for the electrocorticographic and behavior patterns of the waking state. While high frequency electric stimulation of the cephalic portion of this structure causes the awakening of the sleeping cortex, an injury produced in the same area causes a state of irreversible sleep.

According to recently acquired knowledge in neurophysiology, this system amplifies and transmits stimuli to the cortex; the stimuli from the corticipetal pathway, bearing the various afferent impulses, are discharged at this point via the collateral fibers, thus inducing in the cortex itself that state of wakefulness that constitutes the physiologic substratum of conscious perception.[25, 28]

Thus, recent electrophysiologic studies have shown that afferent impulses, originating from stimulation of the peripheral somatic and visceral receptors, are carried to the cortex via two different systems: the first represented by the long sensory pathways, the second by the brain stem reticular formation.

But, whereas in the former system every sensory stimulus is conveyed via a distinct pathway and projects itself into specific cortical areas, in the latter the different afferent sensory and sensitive stimuli are conveyed haphazardly, and cortical projection is not selective but diffuse.

Furthermore, the reticular reactions have a long period of latency, and when the stimuli are in rapid succession, their amplitude progressively decreases; on the other hand, in the sensory pathways, latency is short, and there is no reduction of the amplitude in the reactions produced close together.

French et al,[25, 26] in studying the effects of ether and barbiturates on the ascending path-

way in the medial reticular formation and the lateral sensory pathways, have observed that the potentials produced in the latter from afferent stimuli, as well as the initial occurrence of the primary cortical reaction, are not modified by such anesthetics. On the contrary, the potentials produced in the reticular formation of the mesencephalon and the more retarded occurrence of the cortical reaction present a great sensitivity to the depressant action of the barbiturates and ether. Thus, according to these authors, the lessening of the activity of the multisynaptic cortical and subcortical structures would share in the production of the state of anesthesia to a considerable degree.

The observations of French et al have been confirmed by the studies of Arduini and Arduini,[3] from which has been further proved the marked sensibility of reticular formation of the encephalic stem to metabolic alterations and the action of stimulating drugs.

Following the technique of the above-mentioned authors, we have studied the influence that chlorpromazine is able to exert on the ascending pathway in the reticular formation.

On the basis of the results obtained, we can affirm that the intravenous administration of chlorpromazine in a single dose of 1 to 3 mg./Kg. is sufficient to produce a marked reduction of the amplitude of the reticular reactions evoked by acoustic stimulation or by single shocks applied to the central stump of a sciatic nerve.

The dosage of 5 mg./Kg. (fig. 4) completely abolishes these reactions while it modifies neither the potentials produced in the sensory pathways nor the primary cortical reaction, which remains unchanged in its components; this is also true of markedly higher dosages (10 mg./Kg.).

Together with the lessening of the reactions, one observes a progressive rise in the threshold of the electric stimulus of the reticular formation of the mesencephalon with respect to the cortical state of wakefulness in the *encéphale isolé* preparation (fig. 5). Dosages higher than 10 mg./Kg. abrogate the cortical reaction of wakefulness due to reticular electric stimulation; as mentioned above, these dosages are as yet ineffectual in modifying the primary cortical reactions to afferent stimuli.

It should be noted that the dosage of chlorpromazine necessary to block the reticular formation is considerably lower (5 to 7 mg./Kg.) if it is simultaneously administered with a dosage of pentobarbital sodium (5 mg./Kg.), which by itself is not able to induce a reticular block.

These results, while clearly proving the marked sensitivity to chlorpromazine of the reticular formation of the mesencephalon, show that on this level barbiturates and chlorpromazine are capable of mutual potentiation.

EFFECTS OF CHLORPROMAZINE ON CORTICAL ACTIVITY INDUCED BY LOCAL APPLICATION OF ATROPINE AND ACETYLCHOLINE

The local application of atropine on the cerebral cortex is able to modify the primary reactions and produce local discharges characterized by mono- or diphasic spikes of high voltage that recur at times in groups of 4 or 5 and at times singly.

Bremer and Chatonnet[9] have described the intensification of the primary cortical reaction in the auditory system. Chatfield and Purpura[17] have observed that such an effect appears with greater ease with low concentrations of atropine, capable simultaneously of

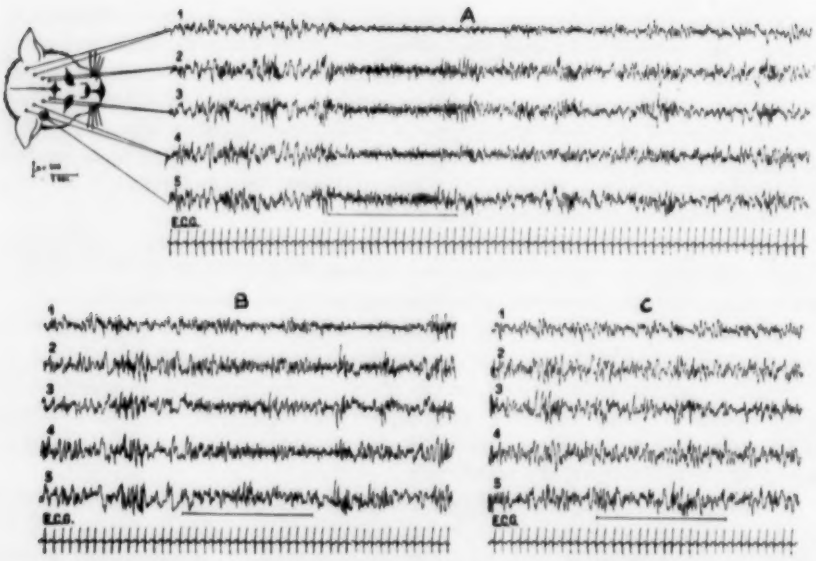


FIG. 5. Effects of high frequency electric stimulation of the reticular formation of the mesencephalon upon the electroencephalogram (1, 2, 3, and 4) and the electrocorticogram (5) of the *encéphale isolé* cat before (A) and after intravenous administration of 2 mg./Kg. (B) and of 10 mg./Kg. (C) of chlorpromazine. The dark line indicates the duration of the electric stimulus (200 cycles/second; 2 milliseconds; 0.65 volt). Note that in (B) the reaction of the waking state is diminished; in (C) it has disappeared. E.C.G. = electrocardiogram.

causing changes in spontaneous cortical activity; namely, convulsions with the appearance mentioned above.

The local application of acetylcholine on the cerebral cortex, previously treated with neostigmine also applied locally, has a twofold and antagonistic effect on the primary acoustic reactions, sometimes enhancing them and increasing their amplitude, at other times lessening them and causing a reduction of their voltage.

In all the sensory cortical areas, with the exception of the striated zone, acetylcholine further causes after a certain time the appearance of continuous spikes (acetylcholine waves) that can be recorded on the electroencephalogram.[17]

Such local effects of atropine and acetylcholine have been constantly registered in our experiments, which were conducted in the primary acoustic area chiefly.

In general, the effects of atropine (atropine sulfate in 2 per cent solution) began to be observed 5 to 10 minutes after its application, and it was noted that these effects lasted for a long time afterward. The acetylcholine waves, on the other hand, were slower to appear; in our experiments they were apparent 20 to 30 minutes after the application of acetylcholine (acetylcholine chloridrate in 2 per cent solution) on the cortex treated with neostigmine for 10 minutes (neostigmine chloridrate in 2 per cent solution). Moreover, the effect resulting from the application of acetylcholine was of much shorter duration than that due to atropine.

We are still far from an exact knowledge of the cortical mechanisms by which acetylcholine and atropine display their pharmacodynamic action. Evidently this problem is strictly connected with that more general and still obscure problem of the ways of conduction and diffusion of the nervous stimuli through the synaptic systems of the complex circuits and the numerous pathways of the cerebral cortex.

However, in the light of the electrophysiologic and pharmacodynamic studies that have been made to date, it is possible to explain the electric phenomena observed after topical cortical application of these two drugs by assuming the existence of two fundamental mechanisms: cortical and cholinergic mechanisms (according to Marrazzi and Hart[36, 37]) which regulate that cortical function expressed electrically by the primary reaction.

Recently Chatfield and Purpura[17] have admitted the existence of a cortical inhibitory

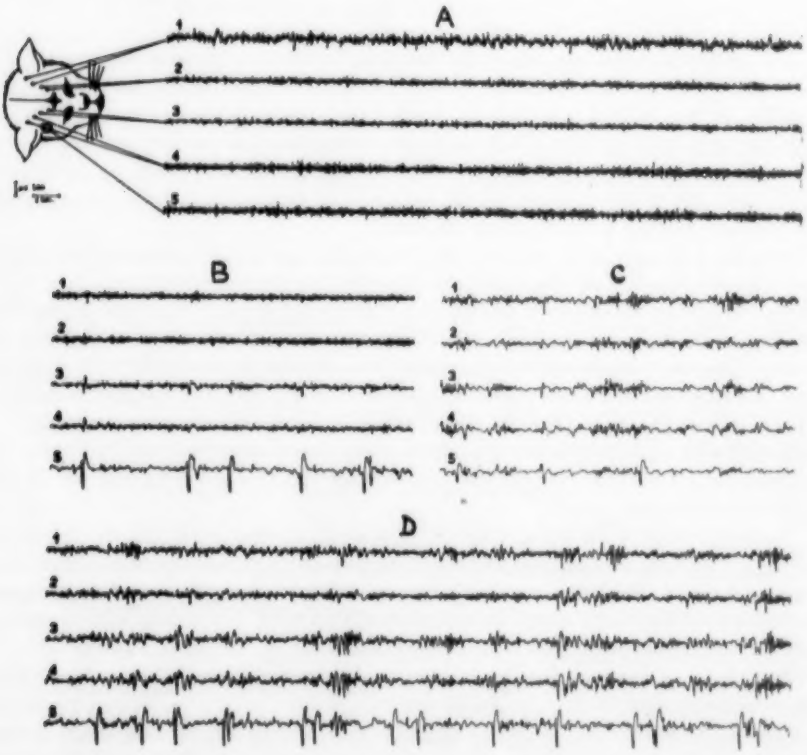


FIG. 6. Electroencephalograms (1, 2, 3, and 4) and electrocorticogram (5) of a waking cat under the influence of curare (A). B: Activity induced by topical application of atropine sulfate (2 per cent solution) arising in the primary acoustic area previously treated with topical application of chlorpromazine in 2 per cent solution. C: Thirty seconds after injection of 2 mg./Kg. of chlorpromazine. Note the diminishing frequency and amplitude of the atropine waves concomitant with the diminished cortical electrogenesis. D: Four minutes after the injection.

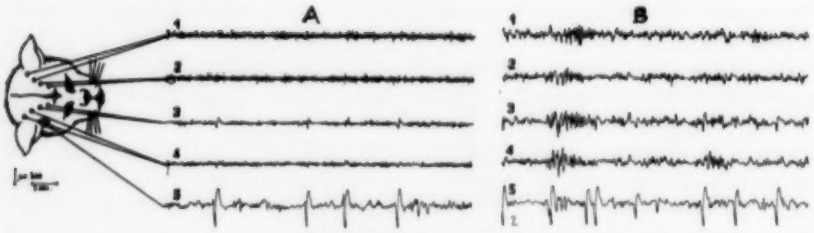


FIG. 7. A: Cortical activity induced by topical application of atropine sulfate (2 per cent solution). B: Thirty seconds after the slow intravenous administration of 2 mg./Kg. of chlorpromazine.

mechanism surmised by Bubnoff and Heidenhain[11] in 1881 and later also asserted by Hunt[29] on the basis of pathologic studies, and by Jung and Tönnies.[31]

This inhibitory mechanism apparently fnnctions by means of nervous elements set in derivation on the synaptic pathways (which represent the other cortical mechanism) responsible for the diffusion in a determined area of the impulses originating in the thalamus or in the opposite hemisphere as well as for the stimulation of the neurons responsible for the corticipetal discharge. Because the same corticipetal stimuli activate the inhibitory mechanism, the result is that in normal conditions its neurons limit the diffusion of the impulses and regulate their corticipetal discharge.

If we admit the cholinergic nature of the two mechanisms and, in agreement with Chatfield and Purpura,[17] admit the sensitivity to atropine of the inhibitory mechanism, it is possible to explain the effects of atropine and of acetylcholine itself. The local application of atropine on the cortex increases the primary reaction and makes it to a great extent diphasic, because it suppresses the inhibition of the diffusion of the stimulus in the cortical area and its conduction to the corticofugal neurons; for this very reason it lowers the convulsion-stimulating threshold to the electric stimulus, as Obrador et al[39] have proved; it is able of its own accord to produce hypersynchronous electric manifestations (appearance of spontaneous atropine spikes); and last, it causes acetylcholine to act on only one of the two cortical systems.

Twofold, instead, is the action of acetylcholine on the cerebral cortex, and for this reason its topical application sometimes produces an increase of the primary reaction and at other times a decrease. The latter is evidently connected with the intensification of the atropine-sensitive system revealed in the electroencephalogram by a spontaneous and continuous discharge of characteristic spikes (acetylcholine waves).

The study we made to investigate possible pharmacologic antagonisms or synergisms between chlorpromazine on the one hand and atropine and acetylcholine on the other aimed at proving whether or not the former substance acts on those cortical mechanisms responsible for the regulation of the conduction of the impulses from the thalamus to the cortex and for their diffusion into the primary area and for the corticofugal discharge. Such mechanisms have been experimentally intensified in order to make the electrophysiologic investigation possible.

In the course of our research we have studied: (1) The effect of local application of chlorpromazine (2 per cent solution) on the atropine hypersynchronous activity and on the

acetylcholine waves, obtained by previous topical application of these substances. (2) The effects of the intravenous administration of the drug on the various cortical activities as mentioned above.

In many experiments, arterial pressure was checked simultaneously with the course of the experiment by means of a mercury manometer connected with the femoral artery.

The results are briefly summarized in the following points: (1) The topical application of chlorpromazine in 2 per cent solution does not prevent or delay the appearance of the spikes due to atropine and acetylcholine; it does not change the epileptogenic effect of these substances previously applied (fig. 6B). (2) The rapid intravenous administration of 2 to 5 mg./Kg. of chlorpromazine causes a swift diminution of spontaneous cortical activity concurrent with evident reduction of all convulsive activity to the point of complete abolition. Such a change is transitory and is exactly coincident with a short-lasting fall of arterial pressure (fig. 6C). With the return of the blood pressure to values little inferior to the initial ones, we observed the concurrent return of spontaneous cortical activity with the typical rhythm of sleep and the reappearance of the atropine and acetylcholine spikes (fig. 6D).

These effects are considerably reduced if a very slow intravenous injection of 2 to 3 mg./Kg. of the drug in a very diluted solution is administered. In this instance, in fact, the fall of the pressure values is much less marked and the spontaneous cortical activity does not show an evident decrease of the voltage (figs. 7, 8). Furthermore, the transition from the

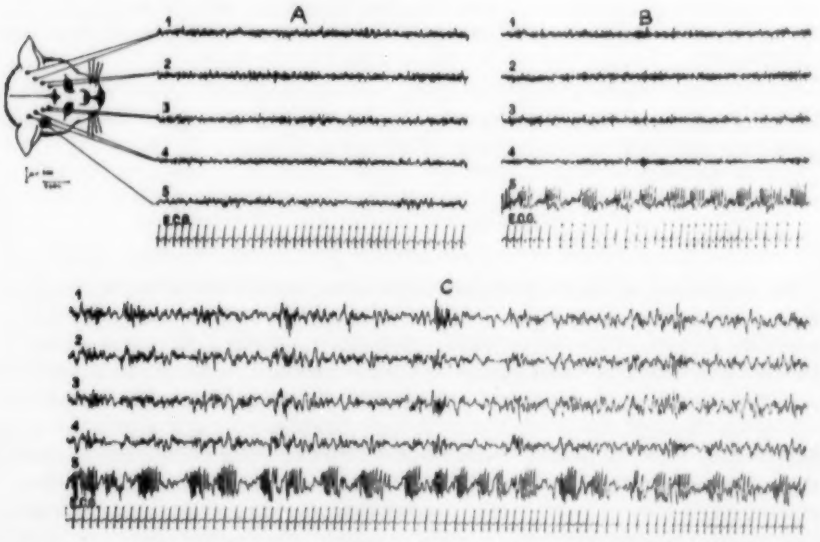


FIG. 8. Electroencephalograms (1, 2, 3, and 4), electrocorticogram (5), and electrocardiogram (E.C.G.) of the waking cat under the influence of curare (A). B: Activity induced by topical application of acetylcholine chloridrate (2 per cent solution) upon the primary acoustic area of a cat previously treated with topical application of neostigmine methylsulfate (2 per cent solution). C: Same as in (B) four minutes after slow intravenous administration of 4 mg./Kg. of chlorpromazine.

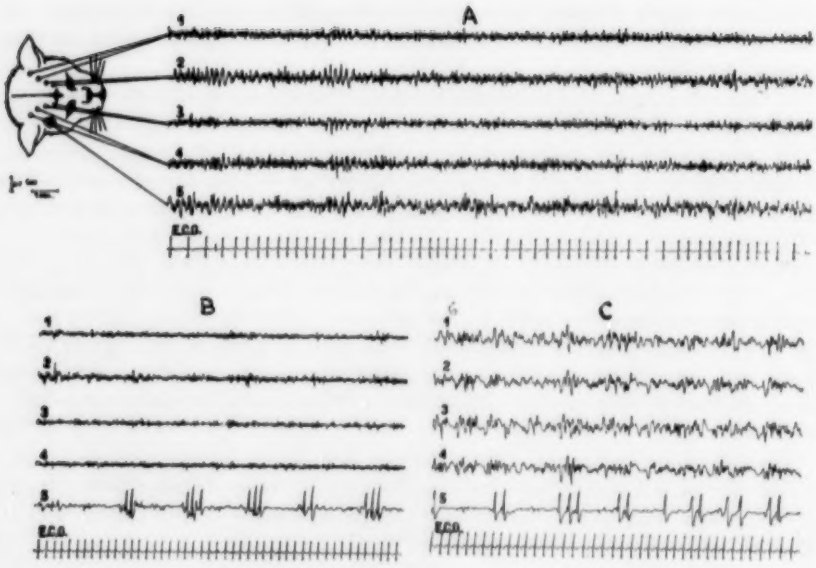


FIG. 9. A: Same as in figure 8. B: Local convulsive activity due to topical application of strychnine nitrate in 0.5 per cent solution. C: Same as in (B) four minutes after slow intravenous administration of 5 mg./Kg. of chlorpromazine.

lively diagram of the waking state to the synchronized one of sleep occurs gradually after passing through a phase of retardation of the activity of the bases.

EFFECTS OF CHLORPROMAZINE ON THE ACTIVITY INDUCED BY STRYCHNINE APPLIED LOCALLY ON THE CORTEX

We have studied the effects of chlorpromazine on the local convulsive activity produced by local application of strychnine in various concentrations (0.5 per cent, 1 per cent of strychnine nitrate). The results of these experiments, performed under various conditions (cats *encéphale isolé*, cats nonanesthetized and immobilized by curare, and cats anesthetized with barbiturates), are absolutely uniform in showing that chlorpromazine does not influence the cortical discharge due to strychnine. In fact, the preparatory local application of the drug does not affect the period of latency (which differs according to the concentrations of strychnine used) that occurs between the strychninization of the cortex and the appearance of the first spikes; nor is it able to affect the convulsive discharge present when chlorpromazine is applied after the strychnine.

The intravenous administration of chlorpromazine in the various dosages mentioned in the previous experiments seems at first glance to inhibit the strychnine spikes temporarily. However, it is sufficient to check the arterial pressure to note that the temporary disappearance is strictly connected with the initial fall of pressure. In fact, the subsequent return

of the arterial pressure to normal values coincides with the spontaneous return of convulsive cortical activity. On the other hand, if chlorpromazine is injected slowly in order to avoid a too abrupt fall of pressure, the blocking of the strychnine spikes does not occur or is considerably reduced (fig. 9).

The efficient synchronization of the nervous impulses is more responsible than the degree of excitability of the single neurons for the formation of the convulsive discharges due to strychnine, as is also shown by the occurrence of strychnine spikes in the condition of cortical depression. For this reason, the absence of the inhibition of the convulsive discharges does not in itself weaken the hypothesis that the depressive action of chlorpromazine could be exerted on a cortical level also.

This hypothesis gains value if we consider at the same time what has been reported above; namely, that this drug does not change the components of the primary cortical reaction. In this way, then, it is also demonstrated that not only the synchronization of the nervous impulses but also the degree of excitability of the cortical neurons is exempt from the influence of the drug itself.

DISCUSSION AND CONCLUSIONS

The pharmacologic action of chlorpromazine on the autonomic nervous system has been documented by this time by a series of studies.

According to Courvoisier et al,[18] who were the first to conduct a systematic investigation of chlorpromazine, this drug has a depressant action on the sympathetic as well as on the parasympathetic nervous system, as is shown by the modification of some of the reflexes of the autonomic nervous system produced experimentally in the vagal and cervical sympathetic orbit after administration of chlorpromazine. These authors, in fact, have observed that in such conditions cardiac arrest and the fall of pressure upon stimulation of the peripheric stump of the vagus fail to occur; there is marked depression of the carotid sinus and vasodepressor reflexes produced by the occlusion of the common carotid arteries, and there is diminution of the hypertensive effect due to stimulation of the central stump of the vagus nerve.

Kopera and Armitage[32] have proved in some biologic tests the antiadrenalinic, antiacetylcholinic, and antihistaminic action of chlorpromazine, thus agreeing with what had already been established by Courvoisier et al[18] in their studies.

The research work of De Risio and Urbani,[24] undertaken with the intention of studying the behavior of cholesterol in the adrenal gland after electroshock (in guinea pigs treated with ganglioplegic substances, among which was chlorpromazine), and the work of Saginario[40] on the variations of the sedimentation rate in individuals subjected to the action of chlorpromazine, indirectly confirm its action on the autonomic nervous system with which the mechanisms of neurohormonal integration are naturally strictly connected.

Although some of the effects produced by chlorpromazine must be attributed without any doubt to its antiadrenalinic and antiacetylcholinic action on the ganglionic level or on the ortho- and parasympathetic effectors, for the explanation of some other effects we have to admit a depression of the medullary and diencephalic centers.

In this direction are pointed the studies of Cathala and Pocidalo,[14] who have observed deep sleep, hypothermia, and the failure of hypertensive reaction due to stimulation of the

central stump of the vagus and to occlusion of the carotids in animals that had been injected with 2 mg./Kg. of chlorpromazine, the drug being injected into the cerebral ventricles. Similarly, Dasgupta and Werner[19] maintain that the drug has a central action in blocking the vasomotor reactions. In the experiments of these research workers, the fall of arterial pressure and the suppression of the carotid sinus reflex occurred after an intracisternal injection of chlorpromazine. In the decorticated cat, injected with 50 to 100 mg./Kg. of chlorpromazine, the pressure reactions after electric stimulation of the hypothalamic and medullary areas do not occur, whereas such effects are obtained in the normal condition.

On the other hand, the negative results obtained by Holtzbauer and Vogt[28] in connection with the action of chlorpromazine upon diencephalic and sympathetic activity do not, in our opinion, invalidate what has been reported above because of the great possibility of inadequate technique in their experiments, which were undertaken in order to evaluate certain effects of the drug on specific centers of the diencephalon independently of the previous influence of other substances.

The pharmacologic properties of chlorpromazine have been studied also in other central and peripheric sections of the nervous system. Courvoisier et al[15] and Kopera and Armitage[32] have observed a local anesthetic action, which, according to the two latter authors, would seem to be superior to that of procaine. The action of chlorpromazine on the central nervous system, however, appears far more interesting. In this area it has an action that has elicited theoretical questions of remarkable interest in connection with physiologic and physiopathologic conceptions, and its effect justifies the extensive use of this drug in the neuropsychiatric field.

The administration of chlorpromazine in adequate dosages induces, in human beings and animals, drowsiness followed by sleep after gradual subsidence of the waking state. The state of sleep is light, requiring a quiet environment, and it can be interrupted by stimuli of even low-grade intensity. In the immediately preceding stage the changes of the waking state (torpor, disorientation, and abulia) are less accentuated than those we observe after administration of barbiturates.

Dasgupta and Werner[19] have observed that in the rhesus monkey dosages of chlorpromazine, ineffectual in producing sleep, interfere with the state of aggressiveness typical of the rhesus monkey's habitual behavior at the sight of human beings. Thus, animals that are difficult to handle prior to the administration of the drug become extremely quiet and docile after the administration. As regards higher dosages, a similar effect is observed in the first moments; later this effect is not easy to recognize because of the torpor, drowsiness, and the state of sleep into which eventually the animal falls. Even more significant than this point seems the disappearance of the "sham rage," described by the authors in the thalamic cat after administration of chlorpromazine.

The tranquilizing and hypnogenic action of the drug is clinically associated with hypotonia, which could not easily be attributed to the paralyzing effect that the drug exerts directly on the striated muscle and on the neuromuscular preparations;[32] as we shall see later, there are sufficient proofs to enable us to assume that hypotonia depends more probably on the central action. This is already apparent from the clinical effects of the drug, but it is still better documented by the electroencephalographic recording.

The changes of the electric cerebral activity following administration of chlorpromazine have been studied in human beings by Terzian,[44] Carreras and De Risio,[12] and others; by

Dasgupta and Werner[19, 20] in the monkey; by Cazzullo and Guareschi[15] in the dog; by Angeleri et al,[2] Dell and his collaborators (1954), and Balestrieri and Fadiga[4] in the cat; and, finally, by Terzian and Ruberti[45] in the rabbit.

Since 1952 Terzian, having noted the identity of the electrographic phases in sleep due to chlorpromazine with those of spontaneous sleep and on the basis of the recent electrophysiologic discoveries of Moruzzi and Magoun,[35] has formulated the hypothesis that the location of action in the central nervous system of this drug is the reticular formation of the encephalic stem. Carreras and De Risio,[13] Sanguineti et al,[41] and Dasgupta and Werner[19, 20] have concurred in this point of view on the basis of identical observations, made from diagrams of human beings and monkeys respectively, of electrographic similarity between spontaneous sleep and that induced by chlorpromazine.

Furthermore, in 1954 experimental corroborations were made by many authors relating to the depressant action of chlorpromazine on the reticular formation of the brain stem.

Angeleri et al,[2] at the same time as Hiebel et al,[27] have described the abatement of reactions produced in the reticular formation by sensory stimuli. Some time later, Balestrieri and Fadiga,[4] studying the pattern of the reaction in the waking state to repeated electric stimulation of the sciatic nerve of the cat, observed that it is markedly reduced or abolished when adequate dosages of chlorpromazine are injected intravenously.

The experimental work that we carried on with this drug for more than a year, comprehensively reported in the present paper, offers distinct corroboration of what has been stated previously.

On the other hand, the experiments of De Risio and Manghi[23] have demonstrated that chlorpromazine is extremely active in abolishing rigidity due to decerebration. It is known that the reticular substance of the stem of the encephalon constitutes a regulatory center of the muscular tone (Magoun and Rhines, 1947). Thus, the power of the drug to abolish the extensory hypertonia of the decerebrated animal must be attributed to its depressant action on this regulatory tone center.

In conclusion, all experimental data from studies aimed at investigating, within the present possibilities of research, the activity of the reticular formation of the brain stem point to the fact that it undergoes a depressant effect due to chlorpromazine. In fact, not only the electric potentials elicited in the reticular formation by sensory stimuli, but also those known effects that operate at a distance (reaction of arrest and extensory rigidity from decerebration), are either reduced or abolished.

According to Longo, Van Berger, and Bovet (1954), the action of chlorpromazine on the nervous system would seem to be effected by way of a block at the synapsis level. It is thus easy to imagine that the electivity of the drug for the reticular formation depends on the great number of interneuronal synapses present in this structure.

In addition, the clinical data that have been accumulating in recent years indicate a therapeutic effect of the drug in those diseases or in those symptoms that, according to the most recent advances in physiopathology, must be attributed to a great extent to a dysfunction of the reticular system of the brain stem.

We shall include among the mental diseases that benefit from the use of chlorpromazine the hypomanic and manic states, the syndromes of confusion, posttraumatic psychosis, alcoholic psychosis, and toxicopathic conditions. We observe in these cases, when chlor-

promazine is used, a general sedative effect with a progressive return of consciousness to a normal state while the ability to think gradually returns (Chatagnon and Chanoit,[16] Delay et al,[21, 22] Macchi et al,[32] Maroncelli, etc.).

In the neurologic field, chlorpromazine has proved particularly useful in reducing spastic hypertonicity and abolishing hypertonicity and concomitant clonicity (Manghi;[26] Sigwald and Bouttier;[43] Basmajan and Szatmazi, 1955); in the hypertonicity of Parkinson's disease a reduction of the muscular tone has also been obtained;[5] and last, the drug is equally efficacious in choreic and parkinsonian hyperkinesis.[5, 33]

At this date it is reasonable to ascribe the pathogenesis of these latter syndromes to the reticular formation in accordance with the studies of McCulloch et al,[34] of Schreiner et al,[42] of Peterson, Magoun, McCulloch, and Lindsley (1949), and of Jekner and Ward.[30] Thus, while the use of chlorpromazine in the above-mentioned conditions is warranted on theoretic grounds, its efficacy in reducing or abolishing the manifestations of these conditions represents an indirect proof of the validity of the experimental results.

At this point a question arises relative to the possible direct action of chlorpromazine on the cerebral cortex. Cazzullo and Guareschi,[15] although admitting the action of the drug on the reticular formation, do not exclude the possibility that it may act on other nervous structures, particularly the neopallium.

These authors think that chlorpromazine-induced sleep should be considered a result of the depressant effect on all the nervous structures involved in the mechanism of sleep. In support of this theory they cite the reservations made by Bremer[10] concerning the theory of spontaneous and provoked fluctuations of the system of reticular activity. It is known, in fact, according to Bremer, that the cerebral cortex with its sensitive and sensory areas of projection would seem to assume an important role in determining the cessation of sleep.

Courvoisier et al[18] have observed the disappearance of the conditional reflexes in the rat after administration of chlorpromazine, although the motor efficiency of the animal was not yet involved.

Finally, according to Baruk et al,[6] this drug would seem to have an elective action on the cortex because it is able to produce effects that are the more marked—to the point of eliciting a catatonic state—the higher the degree of the phylogenesis of the animal, that is, the more its neopallium is developed.

A great part of our experimental study has been concerned with ascertaining whether chlorpromazine is able to produce changes in the electric cortical activity.

In order to avoid interference in the neopallium by subcortical structures, we have used the drug in local application also, which in general has been shown to be a very effective way to reveal the pharmacodynamic action of substances capable of influencing the activity of the cortex.

As we have shown in the preceding pages, this investigation dealt with those electric manifestations that, according to the most recent experimental advances and the most creditable hypotheses to date, are the most tangible expression of the diffusion of the nervous impulses through the synaptic systems of the complex circuits and of the numerous pathways of the cerebral cortex.

The lack of any change in amplitude and pattern in the electroencephalogram of the primary cortical reactions after topical application of chlorpromazine in the acoustic area

warrants the conclusion that chlorpromazine is not able to modify the conduction of the nervous impulses from the thalamus to the cortex or their diffusion in the primary zone and their corticofugal discharge. It is also not effective in changing in any way the intensification of these phenomena as obtained by the effect of strychnine or by the blocking through atropine of the inhibitory system as described by Chatfield and Purpura.[17] Finally, the lack of any change in the acetylcholine waves, obtained after local application of chlorpromazine, proves that the activity of this inhibitory system is also not influenced by this drug. The differences in the electroencephalogram as shown during sleep induced by chlorpromazine and the barbiturates, respectively, as previously discussed, indirectly lead us to conclude that chlorpromazine does not have a direct effect on cortical activity, which effect the barbiturates instead typically have.

On the other hand, the changes we observe in the cortex, following small dosages of the drug administered in rapid intravenous injection, should not mislead us, because the ephemeral disappearance or diminution of all activities is undoubtedly related to the diminished electrogenesis of the cortex caused by a rapid fall of pressure. These effects, in fact, are not present if the intravenous injection is given very slowly, and consequently the hypotensor effects are much less abrupt. Neither should we be misled by the slow rhythms of sleep observable in the electroencephalogram, because they are induced by the depression of the subcortical structures on which chlorpromazine has been shown to act most markedly.

Finally, we will not use further words, after what has been stated previously, to interpret the changes that the afterdischarge of the primary cortical reactions is exposed to following intravenous administration of chlorpromazine. In this instance, also, many things point to an indirect and not a primary effect exerted by the drug on the cortex, which, among other things, retains unaltered the characteristics and the voltages of its primary reaction.

In summing up, the data of our experiments lead to the conclusion that a direct action of chlorpromazine on the neopallium is not established. This is in agreement with other research studies of the same kind.[4]

We are, of course, far from thinking that the electrophysiologic study is able to interpret all cortical functions directly obtainable by experimental investigation. Such investigation, in fact, comprises only one aspect of the activity of the neurons. We cannot exclude the possibility, either, that further research and technical progress by supplying other data may lead to different interpretations. The fact remains, however, that while the electrophysiologic results at our disposal warrant the conclusion that chlorpromazine has no direct action on the cerebral cortex, which is indirectly influenced by deep-seated structures sensitive to the drug, there are no decisive proofs of any other nature that would seem to point to the contrary view.

In attempting to establish the center of action of a certain substance within a chain of interdependent systems, it is very important to ascertain whether manifestations at a certain level are not to be attributed to other structures. For this reason we do not think that our opinion can be invalidated by the interpretation some authors give to experiments that have no relation to the electrophysiologic field. The disappearance of the conditional reflexes and the effects in various animals after administration of chlorpromazine, observed respectively by Courvoisier et al[15] and by Baruk et al,[6] can be interpreted without necessarily having to admit an elective action of the drug upon the cortex and consequently without being obliged to deny the electrophysiologic evidence.

SUMMARY

The authors have studied the effect of chlorpromazine as expressed in the electroencephalogram on the cortical and reticular reactions to afferent stimuli, and on electrocortical activity induced by the local application of strychnine, acetylcholine, and atropine in the cat under various experimental conditions.

On the basis of the results obtained in the experiments, the authors assert that chlorpromazine influences the central nervous system and that the elective site of action can be identified as the ascending reticular formation of the brain stem.

BIBLIOGRAPHY

1. Allen, W. F.: Origin and estimation of the secondary visceral fibers in the guinea pig, J. Comp. Neurol. *35*:275, 1923–1924.
2. Angeleri, F.; Carreras, M., and Urbani, M.: Modificazioni indotte dal 4560 R.P. sui potenziali evocati registrati nella formazione reticolare del tronco dell'encefalo e nella corteccia cerebrale, Riv. neurol. *24*:702, 1954.
3. Arduini, A., and Arduini, M. G.: Effect of drugs and metabolic alterations on brain stem arousal mechanism, J. Pharmacol. & Exper. Therap. *110*:76, 1954.
4. Balestrieri, A., and Fadiga, E.: L'azione del largactil e dell'antipar sui sistemi di proiezione corticale, Boll. Soc. ital. biol. sper. *30*:1241, 1954.
5. Balestrieri, A., and Montanari, M.: Sull'azione del largactil (4560 R.P.) nelle sindromi parkinsoniane, Rassegna di neurol. veget. *10*:395, 1953.
6. Baruk, H.; Laudy, J., and Bergès, J.: La thérapeutique par la chlorpromazine, Ann. méd.-psychol. *113*:705, 1955.
7. Berry, C. M.; Karl, R. C., and Hinsey, J. C.: Course of spino-thalamic and medial lemniscus pathways in the cat and rhesus monkey, J. Neurophysiol. *13*:149, 1950.
8. Bremer, F.: Le problème physiologique du sommeil, Medicina *5*:589, 1951.
9. Bremer, F., and Chatonnet, J.: Acetylcholine et cortex cérébral, Arch. internat. de physiol. *57*:106, 1949.
10. Bremer, F., and Terzuolo, C.: Rôle de l'écorce cérébrale dans le processus du reveil, Arch. internat. de physiol. *61*:86, 1953.
11. Bubnoff, N., and Heidenhain, R.: Ueber Erregungs und Heunnungsvorgänge innerhalb der motorischen Hirncentren, Pflüger's Arch. f. d. ges. Physiol. *25*:137, 1881.
12. Carreras, M., and Angeleri, F.: Sull'azione centrale del potenzializzatore 4560 R.P., Boll. Soc. ital. biol. sper. *31*:474, 1955.
13. Carreras, M., and De Risio, C.: Modificazioni del tracciato elettroencefalografico sotto l'azione del largactil, Ateneo parmense *24*:734, 1953.
14. Cathala, H. P., and Pocidalo, J. J.: Sur les effets de l'injection dans les ventricules cérébraux du chien du chlorydrate de diméthyl-amino-propyl-N-chlorophenothiazine (4560 R.P.). Action centrale de ce produit, Semaine d. hôp. Paris *29*:490, 1953.
15. Cazzullo, C. L., and Guareschi, A.: Influenza di un derivato della fenotiazina (largactil) sull'attività elettrica dell'encefalo di cane, Riv. neurol. *24*:602, 1954.
16. Chatagnon, P., and Chanoit, P.: Psychoplégie transitoire; résultat clinique observé dans les états d'excitation psychomotrice à la suite de l'action d'un dérivé de la phénothiazine, Ann. méd.-psychol. *111*:360, 1953.
17. Chatfield, P., and Purpura, D.: Augmentation of evoked cortical potentials by topical application of prostigmin and acetylcholine after atropinization of cortex, E. E. G. Clin. Neurophysiol. *6*:287, 1954.
18. Courvoisier, S.; Fourner, J.; Decrot, R.; Kolsrey, M., and Koetshet, P.: Propriétés pharmacodynamiques du chlorhydrate de chloro-3 (diméthylamino-3'propil) 10 phénothiazine (4560 R.P.), Arch. internat. de pharmacodyn. et de thérap. *92*:305, 1953.
19. Dasgupta, S. R., and Werner, G.: Changes of behaviour and electroencephalogram in Rhesus monkeys caused by chlorpromazine, Arch. internat. de pharmacodyn. et de thérap. *99*:451, 1954.

20. Dasgupta, S. R., and Werner, G.: Inhibition of hypothalamic, medullaris and reflex vasomotor responses by chlorpromazine, Brit. J. Pharmacol. 9:389, 1954.
21. Delay, J.; Deniker, P., and Harl, M.: Traitement des états d'excitation et d'agitation par une méthode médicamenteuse dérivée de l'hibernotherapie, Ann. méd.-psychol. *110*:267, 1952.
22. Delay, J.; Deniker, P., and Harl, M.: Utilisation en thérapeutique psychiatrique d'une phénothiazine d'action centrale élective, Ann. méd.-psychol. *110*:112, 1952.
23. De Risio, C., and Manghi, E.: Studi sul trattamento farmacologico dell'ipertonia muscolare. Il largactil ed il fargan nel gatto decerebrato, Boll. Soc. ital. biol. sper. 30:1352, 1954.
24. De Risio, C., and Urbani, M.: Influenze di alcuni gangliioplegici sul contenuto in colesterolo dei surrendi di cavia dopo elettroshock, Gior. di psichiat. e di neuropat. *82*:1138, 1954.
25. French, J. D.; Verzeano, M., and Magoun, H. W.: An extralemniscal sensory system in the brain, Arch. Neurol. & Psychiat. *69*:505, 1953.
26. French, J. D.; Verzeano, M., and Magoun, H. W.: A neural basis of the anesthetic state, Arch. Neurol. & Psychiat. *69*:519, 1953.
27. Hiebel, G.; Bonvallet, M., and Dell, P.: Action de la chlorpromazine (largactil, 4560 R.P.) au niveau du système nerveux central, Semaine d. hôp. Paris 30:2347, 1954.
28. Holtzbauer, M., and Vogt, M.: The action of chlorpromazine on diencephalic sympathetic activity and on the release of adrenocorticotropic hormone, Brit. J. Pharmacol. 9:403, 1954.
29. Hunt, J. R.: A theory of the mechanism underlying inhibition in the central nervous system and its relation to convulsive manifestations, A. Research Nerv. & Ment. Dis., Proc. 7:45, 1941.
30. Jekner, F. L., and Ward, A.: Bulbar reticular formation and tremor, Arch. Neurol. & Psychiat. 70:489, 1953.
31. Jung, R., and Tönnies, J. F.: Hirnelektrische Untersuchungen über Enstehung und Erhaltung von Krampfentladungen: die Vorgänge am Reizort und die Bremsefähigkeit des Gehirns, Arch. f. Psychiat. *185*:701, 1950.
32. Kopera, J., and Armitage, A. K.: Comparison of some pharmacological properties of chlorpromazine, promethazine and phethidrine, Brit. J. Pharmacol. 9:392, 1954.
33. Macchi, G.; Manghi, E., and Saginario, M.: Indicazioni e metodi di impiego del Largactil (4560 R.P.) in terapia neuropsichiatrica, Riv. sper. freniat. 78:1, 1954.
34. McCulloch, W. S.; Ward, A. A., and Magoun, H. W.: On components of the extrapyramidal system, Tr. Am. Neurol. A. Ann. Report, p. 93, 1947.
35. Manghi, E.: Il Largactil (4560 R.P.) nelle sindromi ipertoniche e discinetiche, Gior. di psichiat. e di neuropat. *82*:939, 1954.
36. Marrazzi, A., and Hart, E. R.: Adrenergic and cholinergic influences on evoked potentials in pathways of simple synaptic pattern, E. E. G. Clin. Neurophysiol. 2:116, 1950.
37. Marrazzi, A., and Hart, E. R.: Cerebral synaptic responses to drugs as counterparts of possible humoral mechanism, J. Pharmacol. & Exper. Therap. 98:22, 1950.
38. Moruzzi, G., and Magoun, H. W.: Brain stem reticular formation and activation of E. E. G., E. E. G. Clin. Neurophysiol. 1:455, 1949.
39. Obrador, S.; Ortiz, P., and Mandoki, J.: Anticonvulsive action of belladonna and atropine, Arch. Neurol. & Psychiat. 61:84, 1949.
40. Saginario, M.: Variazioni della velocità di sedimentazione delle emazie nei soggetti trattati con il Largactil (4560 R.P.), Gior. di psichiat. e di neuropat. *82*:1107, 1954.
41. Sanguineti, I.; Negri, V., and Laricchia, R.: Modificazioni dell'E. E. G. in malati di mente sottoposti all'azione del Largactil, Riv. neurol. 23:518, 1953.
42. Schreiner, L. H.; Lindsley, D. B., and Magoun, H. W.: Role of brain stem facilitatory system in maintenance of statistics, J. Neurophysiol. 12:207, 1949.
43. Sigwald, J., and Bouttier, D.: L'utilisation des propriétés neuroplégiques du 4560 R.P. en thérapeutique neuropsychiatrique, Presse méd. 61:607, 1953.
44. Terzian, H.: Studio elettroencefalografico dell'azione centrale del Largactil (4560 R.P.), Rassegna di neurol. veget. 9:211, 1952.
45. Terzian, H., and Ruberti, R.: Studio sperimentale dell'azione del Largactil e del pendiomid sull' attività elettrica cerebrale del coniglio, Riv. neurol. 24:686, 1954.

Value of a Therapeutic Trial with Liothyronine

Albert H. Helm, M.D.

COLLINGSWOOD, N. J.

Medical syndromes often attain sudden popularity after years of apparent neglect. Recently the syndrome of metabolic insufficiency has received much attention by clinicians. "Metabolic insufficiency" is a new name for a condition similar to one that has been known[1–3] as "nonmyxedematous hypometabolism," "the hypometabolic state," and "euthyroid hypometabolism."

Metabolic insufficiency is thought to be a form of hypometabolism. "Hypometabolism" is, of course, a blanket term describing a decreased metabolic function that can result from various causes. It may result from a deficiency in the gland's production of thyroid hormone (hypothyroidism, myxedema) or from such comparatively rare factors as adrenal insufficiency, nephrosis, or hypopituitarism.

According to a current theory,[4] hypometabolism may also be caused by an inability to utilize thyroid products; specifically, by an inability to convert L-thyroxine to liothyronine* (L-triiodothyronine), the substance that—as several studies[5–7] indicate—is probably the form of the thyroid hormone active at the cellular level. Theoretically, then, a state of decreased metabolic function can exist even though the thyroid gland may be functioning normally. This theory has been advanced to explain the clinical syndrome of metabolic insufficiency.

Properly speaking, however, there is no fixed "syndrome" characterizing metabolic insufficiency; that is, there is no set of symptoms that regularly occur together and allow one to diagnose the disorder from the patient's presenting complaints. So common and so diverse are the symptoms alleged to accompany metabolic insufficiency that it is extremely unlikely that all will occur in 1 patient and equally unlikely that at least a few of them will not occur in almost all patients. Some of the common signs and symptoms of the disorder are: nervousness, fatigue, lethargy, irritability, headache, muscle and joint stiffness, dry hair and skin, obesity, dysmenorrhea, sensitivity to cold, and facial puffiness.

Because of the almost universal occurrence of these complaints the general practitioner may well suspect that so-called "metabolic insufficiency" is more metaphysical than metabolic and that the term is merely a handy name for grouping together all complaints for which we can find no physical cause. On the other hand, many of the symptoms are similar to those of mild hypothyroidism. Very often a physician sees a patient who would seem to be suffering from mild hypothyroidism but whose laboratory tests fail to reveal evidence of a reduced synthesis or output of thyroid products. If the patient also has a low normal or subnormal basal metabolic rate, he may possibly suffer from metabolic insufficiency.

The following study was undertaken for two reasons. The first, a frankly skeptical one, was to see if metabolic insufficiency existed in any but the most theoretical sense; that is, to determine whether it was an actual diagnostic entity susceptible

---

* The trade name of Smith, Kline & French Laboratories for liothyronine is Cytomel.

to practical treatment in the general practitioner's office. The second reason was to determine—if the disorder did seem to exist—whether a clinical trial with liothyronine might not prove to be a useful method for both treating and diagnosing the condition. This second aim arose primarily from necessity rather than desire. Laboratories capable of giving the required diagnostic tests are too remote for most of my patients to reach easily; the tests themselves cost more than many of my patients can afford.

METHOD

The study was conducted over an 18 month period on 43 patients, all of whom evidenced one or more of the signs and symptoms associated with decreased metabolism. Fatigue, irritability, and nervousness were the most common symptoms; obesity, abnormally dry hair and skin, and brittle fingernails were the most common signs (table I). Except for 2 very lethargic 13 year old children, the patients ranged in age from 25 to 64 years. Their average age was 43 years.

Two patients suffered from hypothyroidism resulting from thyroidectomies. They were included to see if liothyronine might give a better response than was obtained from thyroid. All 43 patients had been previously treated with one or more preparations; 22 had received amphetamine and 33 had received vitamins. Neither of these treatments had been particularly successful. Twenty-five patients had been treated with thyroid. Nine of these (including the 2 patients with postoperative hypothyroidism) had shown a fairly good response. Twelve of these patients had suffered side effects from thyroid: 5 complained of nervousness and tachycardia; 3 of nervousness alone; 2 of tachycardia alone. Three patients had to discontinue thyroid because of side effects.

Basal metabolic rates were taken for 16 patients. The results of all but three tests were in the low normal or subnormal range; that is, from −15 to −30 per cent. The three results that were not low normal or subnormal were +4, −4, and −6 per cent, respectively. Nine of the patients with low basal metabolism were also

TABLE I

Incidence of Symptoms and Signs in 43 Patients

Symptoms and signs	Number of patients
Nervousness	35
Irritability	27
Depression	22
Headache	26
Dysmenorrhea	7
Obesity	38
Fatigue	40
Sensitivity to cold	11
Water retention	14
Dry hair and skin	23
Constipation	25
Brittle fingernails	28

TABLE II

Comparison of Results with Thyroid and Liothyronine (25 Patients)

Degree of response	Drug	
	Thyroid	Liothyronine
Excellent	0	8
Good	9	14
Fair	4	2
Poor	12	1

given protein-bound iodine tests. All results were within the normal range. (The normal range is from 2 to 8 μg.; the range for these patients was from 2.8 to 4.6 μg.)

However, no patient was given liothyronine merely on the basis of laboratory results. The only criterion for giving the drug was that the patient's signs and symptoms indicated that the treatment might be a useful one. The starting dosages of liothyronine ranged from 5 μg. three times daily to 25 μg. twice daily. The maximum daily dosage given was 100 μg. The patients were seen biweekly for periods of from 1 to 12 months. (The average duration of treatment was 23 weeks.)

Because of the metabolic potency of liothyronine, no patient was treated who showed any evidence of Addison's disease or of a cardiovascular disorder. A no-treatment period of one month was allowed to elapse before the drug was given to patients who had been receiving a thyroid preparation.

The patients' responses were evaluated by the following criteria: Excellent: Complete, rapid (within two weeks) relief of most symptoms. Good: Complete, gradual relief of symptoms or a marked relief of symptoms. Fair: Partial relief of symptoms. Poor: No relief.

RESULTS

Thirty-five of the 43 patients had a good to excellent response. The response was excellent in 13, good in 22, fair in 6, and poor in 2.

Liothyronine achieved significantly better results than did thyroid in 22 of the 25 patients who had been previously treated with thyroid. It was of equal value in the other 3. (One of these 3 patients had poor results with both preparations; the other 2 had good results with both.)

Of the 16 patients who received basal metabolism tests, the 13 whose tests were low normal to subnormal achieved a good to excellent response; the other 3 had a fair response.

Two patients suffered undesirable side effects. One developed headaches; the other, dizziness. This last side effect was severe enough to warrant discontinuing the drug.

CASE HISTORIES

The following case histories illustrate each type of response.

Excellent Response.

Case 1. An obese, lethargic girl, aged 14, whose menarche had begun when she was 11, complained of

moderately severe dysmenorrhea, constipation, and frequent headaches. Her parents described her as a "moody, sensitive child." She was stubborn and uncooperative in school and seemed unable to concentrate on her studies. She was irritable and nervous. Another physician had treated her with desiccated thyroid for six months; she had shown no improvement. In early 1955 her basal metabolic rate was −28 per cent; in June, 1956, before the start of liothyronine therapy, it was −25 per cent. She had also been previously treated with amphetamine preparations, but they had increased the degree of her nervousness and the frequency of her headaches.

She was given liothyronine (5 μg. three times daily) and within four weeks all symptoms except the dysmenorrhea were completely relieved. She experienced an, to her, unprecedented feeling of general well-being. She had lost 5¼ pounds. By September, although she had gained weight (2 pounds), and the dysmenorrhea, though less severe, was still present, her marked general improvement had continued. The dosage was increased to 12.5 μg. three times daily. By November she again began losing weight (she lost 3 pounds in that month) and the dysmenorrhea was completely relieved. The most striking result in this patient was her almost complete change from a seemingly indolent, hostile child to an active, friendly one. She is able to concentrate better, and her school work has improved considerably.

Case 2. A 33 year old obese man had been suffering for one year from irritability, constant mild to moderate depression, nervousness, labile blood pressure (thought to be neurogenic), headaches, and general fatigue after moderate exercise. He had discontinued treatment with thyroid and, later, amphetamines because both drugs increased the nervousness and headaches. His basal metabolic rate was −29 per cent; protein-bound iodine was 3.9 μg.

Within 10 days after taking liothyronine he found that his depression was considerably alleviated and that his headaches had ceased. After only five days of therapy he reported a feeling of being well and said, "My old ambition has come back again."

Good Response.

Case 3. A 45 year old woman had suffered from tiredness, somnolence, headaches, moderately severe dysmenorrhea, and constipation. Her hair and nails were brittle, her skin dry. She complained, "I hardly eat a thing, and still I gain weight."

She showed only slight improvement after nine weeks of liothyronine therapy (12.5 μg. twice daily). When the dosage was increased to 25 μg. three times daily, her nails became less brittle; her hair became softer, more manageable; her headaches and constipation disappeared. The dysmenorrhea, though still present, was considerably milder. The medication had no appreciable effect on her obesity. Increasing the dosage to 25 μg. four times daily brought no greater improvement, so it was lowered to 25 μg. three times daily. She has lost only a small amount of weight; however, she now seems to be able to eat fairly liberally without fear of gaining unduly. Like most patients, the most impressive result of therapy, to her, was the fact that she had more energy and that she felt so much better.

Case 4. A 34 year old woman had undergone a thyroidectomy in February, 1953. In August, 1955, her basal metabolic rate was −15 per cent. Before taking liothyronine she had been on thyroid for 18 months. For about a year her response to thyroid had been fairly good, but during the six months previous to being seen by us she experienced a return of signs and symptoms: easy fatigability, irregular menses, depression, headaches, dry skin and brittle nails, and a tendency to gain weight easily.

In December, 1955, she was started on 25 μg. of liothyronine twice daily. Within five weeks she had a menstrual period, for the first time in four months. She was no longer bothered by headaches; her depression had lifted considerably; her skin and nails were normal in appearance. She has maintained this improvement for 10 months on a lower dosage (12.5 μg. three times daily).

Fair Response.

Case 5. A 28 year old woman in the previous three years had suffered from recurrent episodes of obesity in addition to lethargy and headaches. She had been treated from time to time with desiccated thyroid plus amphetamine and had achieved fairly good results. However, if she received thyroid for more than two months she would become extremely nervous and have to discontinue therapy. (Giving amphetamine and thyroid separately identified thyroid as the offending drug.)

On 25 μg. of liothyronine three times daily she has achieved about the same results as she did previously.

(a moderate weight loss and less severe and less frequent headaches). She has, however, been able to continue therapy for, so far, four and a half months without suffering any side effects.

Poor Response.

Case 6. An "always tired" 55 year old man had been suffering from chronic constipation for about 15 years. For six months he had been troubled by frequent headaches. He had dry skin and showed signs of water retention. In 1954 he had been hospitalized for 12 days because of a vertigo of undetermined origin.

After five to seven days of liothyronine (12.5 μg. three times daily) his dizziness recurred, but because his headaches had subsided and he felt better "in general," he continued the drug for an additional five days. His dizziness became more severe, and the drug was discontinued. Two days later the other symptoms had returned.

DISCUSSION

Because of the comparatively informal nature of the investigation, this study cannot be said to prove beyond doubt that metabolic insufficiency is a definite diagnostic entity. However, liothyronine was superior to thyroid in most hypometabolic patients who received both; it achieved good to excellent results in all the patients who had low basal metabolic rates and normal protein-bound iodine tests. (These 9 patients were the only ones who, by the suggested criteria, could definitely be said to suffer from metabolic insufficiency.) But the signs and symptoms evidenced in all these patients and the nature of their response suggest that metabolic insufficiency may well be a diagnostic entity.

There was no doubt that liothyronine was an effective treatment for almost all of these hypometabolic patients. Objective evidence of the drug's efficacy was provided time after time by the lessening or disappearance of such signs as dry hair, dry skin, brittle nails, and facial or other puffiness. But by far the most impressive results were subjective ones—such as the striking increase in energy, the general feeling of well-being, and the disappearance of headaches. Impressive, too, was the rapidity with which the drug acted. Most patients experienced a significant response, either good or bad, within a week (sometimes within a few days) after the drug was begun. When one considers that all these patients had failed on amphetamine and vitamins and that many had failed on thyroid, the possibility that improvement was evidence of a placebo response would seem to be slight.

The success of treatment in the undiagnosed patients indicates that they may have suffered from metabolic insufficiency. It is possible that they may have suffered from other disorders. Several come immediately to mind: borderline hypothyroidism, self-limiting depression, hypochondria. One cannot rule out these possibilities, but in view of the treatment's success, neither can one ignore the fact that many of the complaints may have come from a minor dysfunction in the utilization of liothyronine. Perhaps it is true, as some physicians suspect, that not all our chronic complainers of vague symptoms are neurotics.

The results of this study strongly suggest that if a patient has signs and symptoms of hypometabolism, even if he has failed to respond to thyroid, a therapeutic trial with liothyronine should be carried out.

The satisfying response seen in the majority of these patients indicates that liothyronine is useful as a diagnostic tool. It works rapidly, its effect is not long-lasting, and it is a safe, inexpensive treatment. It can be used first as a substitute for extensive (and expensive) laboratory tests when some elusive metabolic disorder is suspected.

BIBLIOGRAPHY

1. Kurland, G. S.; Hamolsky, M. W., and Freedberg, A. S.: Studies in non-myxedematous hypometabolism. 1. The clinical syndrome and the effects of triiodothyronine, alone or combined with thyroxine, J. Clin. Endocrinol. *15*:1354, 1955.
2. Freedberg, A. S.; Kurland, G. S., and Hamolsky, M. W.: Effect of L-triiodothyronine alone and combined with L-thyroxine in non-myxedematous hypometabolism, New England J. Med. *253*:57, 1955.
3. Watson, B. A.: The hypometabolic state: a clinical entity, New York State J. Med. *54*:2045, 1954.
4. Morton, J. H.: Clinical experience with L-triiodothyronine in metabolic disorders. Scientific exhibit, meeting of American Medical Association, Chicago, June 11–15, 1956.
5. Gross, J., and Pitt-Rivers, R.: Physiologic activity of 3:5:3′ L-triiodothyronine, Lancet *1*:593, 1952.
6. Lerman, J.: The physiologic activity of L-triiodothyronine, J. Clin. Endocrinol. *13*:1341, 1953.
7. Starr, P., and Liebhold-Scheuck, R.: Theory of thyroid hormone action, A.M.A. Arch. Int. Med. *92*:880, 1953.

Basis for Choice of Operation for Cancer of the Breast

The basic surgical concept of an acceptable operation for cure of carcinoma of any organ of the body encompasses two factors. The first is that the local lesion should be resected with an adequate margin of apparent normal tissue about it. The second factor is that as extensive a resection of the field of lymphatic drainage of the carcinoma as is surgically and anatomically practical must be carried out.

When these two factors are applied to operable carcinoma of the breast, it is obvious that there can be no adequate local excision of the local lesion such as one can perform, for example, in carcinoma of the colon. Simple mastectomy, however, could be considered in operable cases as resection of the local lesion with an adequate margin of apparently normal tissue around it.

The second factor, namely that of extensive resection of the field of lymphatic drainage, is the point of dispute that requires further discussion.

The principle upon which radical mastectomy was originally performed was that cancer of the breast generally would spread in an orderly fashion and in one direction, i.e., into the axillary nodes. It is obvious from the description of the lymphatic spread of this disease that this is not true in most of these patients; by the time the patient presents herself for therapy many of the other nodes are involved. Even the ultraradical procedures do not encompass all these avenues of spread in their surgical maneuvers.

Many open-minded surgeons have realized the futility of heroic attempts and are now willing to consider the simpler methods of therapy. Some even go so far as to refuse surgery to patients with certain extensions of the disease who recently were considered operable. Although surgery is undoubtedly the best method available for certain very early localized lesions, the simpler procedures with adequate postoperative radiation therapy seem to be a modality for treatment that has been proved to be adequate and statistically at least as good as radical mastectomy, without the postoperative morbidity and mortality that follow radical procedures. Reports in support of this are appearing in the literature with increasing frequency.—Abstracted from an editorial by Thomas C. Case, Am. J. Surg. *92*:493–495, October, 1956.

I Dreamed that I Dreamed

Nandor Fodor, LL.D.

NEW YORK, N. Y.

The riddle of the dream within the dream reveals many facets that have been neglected by previous investigators. Freud gave generous credit to Stekel for having solved the riddle through the analysis of some convincing examples. The essence of his finding and those of subsequent analysts is that the purpose of placing a dream within the dream is to depreciate its value and rob it of its reality. However, it is not quite easy to follow Freud's wording:

> That which the dreamer continues to dream, after awakening from the dream within the dream is what the dream wish desires to put in place of the extinguished reality. It may therefore be assumed that the part "dreamed" contains the representation of the reality and the real reminiscence, while, on the other hand, the continued dream contains the representation of what the dreamer wished. The inclusion of a certain content in a "dream within the dream" is therefore equivalent to the wish that what has just been designated as a dream should not have occurred. The dream-work utilises the dream itself as a form of deflection.[1]

The difficulty in following Freud's meaning is mainly due to lack of proper terminology. One cannot refer to the dream within the dream and to the continued dream without getting confused about them. I propose to describe the dream within the dream as the inner dream and the other dream that contains it as the outer dream.

Emil A. Gutheil expresses himself with greater but still not sufficient clarity: "According to analytical experience we consider such a mechanism as the dreamer's wish to turn a certain real experience or emotional situation into a dream. It is due to the patient's attempt to make this experience or situation unreal, inaffective."

Applying the terminology proposed, Gutheil says that the content of the inner dream is a pain that we wish to push out of our mind, but as nothing can really be pushed "out," and we cannot hold it in the ordinary dream without waking up from the pressure of the content, we push it inward and make it into a dream. The inner dream therefore is somewhat similar to the fear of a fear, and its main purpose is the same as that of the outer dream: to keep our sleep undisturbed by making the forgetting of unpleasant things easier.

The mechanism is the same as that of the criticism within the dream: "Well, it's only a dream." There are many other ways of minimization. We may defend ourselves against the content of the inner dream by making it into a motion picture fantasy, a news item, a story from a book, or a word like murder, with a complete blank to its background, or we may protect ourselves by waking up from the inner dream but finding ourselves still asleep, in the outer dream. If the pressure of the inner dream is too much to manage we may wake up to reality, breaking both dreams. In order to achieve this complete awakening, a new dream may be necessary: dreaming that we hear our name called by someone (usually a child) who needs us or that the doorbell rings when in reality it did not sound. Another method of defense is

to push the inner dream still further away by making it a dream within a dream within a dream.

Here is an instance of that: "I dreamed I had a dream and was trying to tell you what it was. As I was trying to remember it, I fell back asleep and dreamed that I was in your office telling you the dream. I seemed to be giving it to you in every particular. You were telling me not to waste time on all those little odds and ends, but give you the facts of the story. I got angry and said: that's the way I talk, I have always talked, and will always talk. If you don't like it I am very sorry for you. I was in a terrible rage and left the office."

When every mechanism fails to keep the content of the inner dream from emerging, the patient whips up a rage at the analyst (whose help she seeks) and leaves his office. Not even the attempt of making the dream twice removed has helped. The threefold construction of the dream is re-emphasized by the wording of the dream: the way I talk, have always talked, and will always talk. The reason of the escape was presumably the schizophrenic content of the inner dream, as later events intimated. This patient had a terrible fear of insanity; she could not face that problem even in a dream.

A few clinical instances will illuminate the foregoing and lead up to the consideration of further problems.

The Inner Dream Is a Confession. This is the dream of a woman full of complaints and self pity; her analysis was uncompleted.

"I was lying asleep and the telephone rang. It was Martha, my sister, but her voice was awfully faint. I said: Well, I have been here all the time alone. (But I was aware that this was not true, that B. was with me.) Later, we were together, and she played the piano marvelously. You were her teacher. I thought, I know why; she had every encouragement, and then you can do things, not when you are constantly pulled down."

It is noteworthy that nothing happens in the outer dream. It is bare or barren as the patient's life was. She denies the presence of B., her lover, because he does not fill her life and hurts her. Just before the dream, she had a telephone call from him—and his voice sounded faint and faraway like Martha's in the dream—in which he said that he had failed again and added, accusingly: You are in this, too. In the inner dream the cure for loneliness is an identification with Martha (through the telephone that links them) who is happy-go-lucky and has a husband, a family, and a grandchild. If she were Martha she would have all that. The teacher used to hit her when she did not know the notes, and mother used to be very hard on her for neglecting her piano playing. Now she does not play at all. But Martha does. I teach her. Here is a repressed reproach: nobody loves her, not even her analyst; her life is empty, and she is making no progress.

It was a true confession. She made some progress and stopped being a borderline psychotic, but that was all.

The Inner Dream Conceals the Frightful Truth. An alcoholic patient dreams: "I am doing a trick with a hair. I am trying to keep it straight, suspended in mid-air without holding it. I know I am dreaming and I say that I know magicians do this trick but in reality it cannot happen. I don't quite understand because the un-

conscious mind can do anything in the dream; so why can't I? I have a bunch of hairs, but the hair always falls. I say I am not in control of the events of the dream."

What the patient really could not control was his passion for alcohol. The night before the dream he saw *Ahaunting We Go* with Laurel and Hardy. A professional magician does many suspending tricks in the story, including the rope trick. Magic is a wonderful means of solving difficult problems, but it does not work in this case: the hair falls. In the actual dream, nothing is suspended from the hair, but the patient associated with it an ax hanging over his head by a hair. The inner dream, hidden behind "I know I am dreaming," conceals the ax; it is too painful to envisage. The outer dream is casuistic, but it serves an important purpose. By letting the innocent hair fall, the danger from the suspended ax is cancelled: there is no ax above his head because nothing could hold it. Thus the outer dream, over which the dreamer has more control, falls in line with the game of blindman's buff. It wishfully hides the great danger of his alcoholic addiction. (It was a very real one; within two years the patient was dead.)

Deliberately Making up an Inner Dream while Dreaming. Catharsis is illustrated by this dream:

"I have been looking into a hole in the ground in which my grandfather was asleep in his coffin. It was about the size of your room, but not so long and the ceiling was higher. I suddenly realized that I was dreaming and that I should not be dreaming about holes in the ground. So I made the coffin rise up to the sky as if to compensate myself for the bad dream. I watched it and saw a hazy mist high up, the type I saw during masturbation or when my infant brother was buried and tears filled my eyes. I could just see streaks of the sun on each side. I told myself: I have to tell Dr. Fodor about this dream; I purposely sent the coffin up, and perhaps that makes the dream less effective; after all I made it up."

Here we see the painful content of the inner dream in the process of dissolution. The patient had had some nightmares before about holes in the ground. In these dreams, through the agricultural symbolism of the earth, he represented the trauma of his birth. In the present dream he equates birth with death and resolves it. He remembered little about his grandfather, who died when he was between 7 and 9 years old, but he mentioned that his infant brother, for whose death he felt responsible, was buried at grandfather's feet. As the dreamer is reminded of the burial of this infant brother by the similarity of mist to tears, we have reason to assume that his grandfather's coffin is a cover for another, much smaller coffin that brought death and guilt into close association for the first time. His burning desire is to see the coffin of his infant brother ascend to heaven, the place of eternal life, so that his death will be annulled and he will be free of the guilt and fear of it. This desire is indicated by the analytic background of the dream. The hole in the ground is compared with my room and he is dreaming the dream for my benefit. Grandfather is not dead; he is asleep. As the hole, in previous dreams, represented the womb, he is also identifying the fear of death with the fear of birth and death itself with prenatal sleep. Projected into the future, the fear of birth automatically becomes a death fear. In realizing that he should not be dreaming about holes in the ground, he shows himself being disentangled from both.

The dream is interesting technically because it is successful in fusing the inner dream and the outer one into an integrative design.

VARIETIES OF THE INNER DREAM

Let us now consider some general varieties of the inner dream.

Someone Tells Us of a Dream within the Dream. This mechanism makes the inner dream twice removed; hence the denial of the personal content of the dream is twice as strong.

One patient said, "I dreamed that my wife told me that somebody urinated in her mouth in a dream."

The dreamer witnessed fellatio between his parents when he was very young. The experience must have been very shocking, hence the reason for the denial by twofold deflection.

Waking into the Inner Dream. The dynamic tension of the inner dream may be so great that it will usurp the place of the outer dream in order to replace the reality situation with a psychotic one—a possible hint that the patient is a borderline case. This dreamer, indeed, suffered from fears of insanity, had suicidal compulsions, constantly talked to himself, and believed that he heard others talking to him. While it was not exactly a case of hearing voices, it was almost that.

"I dreamed that I shivered all over as if I had my heat stroke. I woke up in the dream and I was crazy. I choked everybody in the family."

He did suffer from heat prostrations. "Everybody" meant his brother Albert, four years older than he, his wife Clementine, and their 4 year old daughter Josephine, who in the dream had the eye of a witch. This recalled the "evil eye," from which his father was supposed to have suffered at one time, and led to the revelation that his mother's name was also Josephine. He read stories of crazy persons who strangled others and raped them.

With these associations it was easy to see that the inner dream revealed criminal sexual fantasies (of both an incestuous and homosexual nature), the fear of the evil eye (one eye shining at him) originating in the fascination with his mother's genitals. Fears of going blind were the natural complement of his voyeuristic transgression.

The dream suggests that awakening into the inner dream is a sign of the failure of repression; hence a psychotic outbreak may be imminent. In this particular case timely therapy had saved the patient from this calamity.

Waking into the Outer Dream. The fading demarcation line between the inner and outer dream may also hint at tension of psychotic proportions. This patient was a 36 year old man, unmarried, who had suffered from paranoid dreams for years. An outlaw, racketeer, or criminal was chasing him all night. In the morning (still in the dream) he looked into the mirror and noticed that his hair had turned gray at the temples. He said to somebody, "I must have aged last night."

The dream was remembered only when, while shaving, he looked into the mirror and said to himself, "I don't think I have grown older." In a flash, the memory of the dream came back.

The patient did not at first realize that he had had a dream within a dream. He had no memory of having returned home or how the rest of the night, after the chase, passed. The night is fantasy; the morning is reality, awakening. He awakens from the inner dream, the nightmare of being chased, into the outer dream, and then turns against the content of the outer dream, by denying that he is getting old as he shaves. This was his favorite excuse concerning young girls, that he was old for them and could not keep pace with them. However, he suspected that he was trying to alibi for himself. Fear may turn one's hair gray. Was he afraid of, and chased by, his unlawful instincts?

The temples are next to the ear. This patient was hard of hearing. Was it the voice of his desire, against which deafness offered a defense? The day before the dream he visited his mother (a psychotic woman) and was conscious of sexual emotions in her presence. The same thing happened when he visited his older sister; hence his chasing dreams strongly suggest flight from himself, and the gray hair in the dream is a hint that he is fighting a losing battle.

DISGUISES

The resistance to the painful content of the inner dream may take structural form in the disguises of the inner dream.

The Inner Dream Is a Story. Change of the outward form of the inner dream makes it less personal and reduces repressive tension. A story, for instance, that we read while dreaming will not arouse the vigilance of the censor. For example:

"It was as if I had been reading a story. Somebody had seen a woman's body dashed against the rocks. When rooms were being assigned to us in the house, no room was given to anybody on that side of the house from which the body could have been seen."

The patient who dreamed this had a horror of corpses. The dream was concerned with this horror. There were indications that the corpse was his mother. He did not permit himself to discover this by a closer look lest he should have to face a much grimmer story: death in the waters as a direct clue to tremendous aggression fantasies in childhood against two brothers antedating and postdating their births. Aggression against the unborn necessarily implies aggression against the maternal body, hence a death wish. But the body dashed against the cruel rocks was really a cover for his Cain complex, so potently repressed that even the form of the inner dream had to be abandoned and the content barely hinted at through a printed story.*

The Inner Dream Is Represented by Sleep Talking. One patient presented another disguise for the inner dream: dreaming of talking in her sleep:

"I dreamed I was talking in my sleep. I was told afterward, but still in the dream, that I was talking about sex and gypsies. I felt ashamed of the things I might have said. Then I was learning to shoot, holding a large gun."

"Told afterward" clearly states that she woke up within the dream; hence the

---

* For full details of this case see my *New Approaches to Dream Interpretation*, pp. 53–91.

sleep talk about sex and gypsies represents her inner dream. The shame she feels about what she might have said reveals the need of strong repression. She associated the gypsies with the Bluebeard ballet in which Bluebeard's wives come back disguised as gypsies. The gun recalled a rifle club and her statement: "Gee, I would like to learn to shoot. There are a couple of guys I would like to shoot."

At the time of the dream, the patient had the opportunity to marry a desirable man. But she was in a way a Bluebeard herself: she had too many lovers and was afraid that her intended would find out about them. The sleep talk well expresssed this fear. She might give herself away, but if she could shoot her previous lovers she would be safe. Behind this superficial content, however, a deeper conflict is hidden. The original Bluebeard was her father. Her real secret was the relationship with him. The large gun is a hint at the larger object of her hatred. But while she may dream of shooting her lovers fairly freely, she could not dream of shooting her father undisguised. So she chose talking in her sleep, for which she could be held least responsible.

The Inner Dream Is a Fantasy. A homosexual teacher dreamed:

We were on a school trip on a boat. (Every year we take one to Bear Mountain, some years we take two.) The pupils were well behaved, although I had anticipated trouble. (They had misbehaved on one trip, after an anonymous letter to the principal denouncing two homosexual teachers.) At one point in the dream I fantasied the students getting on one side of the boat and rocking it back and forth. It could not have happened. My impression is very strong that they behaved well."

The excursion boats to Bear Mountain are too big to be rocked in the manner described; hence the fantasy of rocking is a dream within the dream. When asked for associations with rocking boat, the patient recalled a story from India. On the Ganges a boat was passing under a tree. An enormous snake jumped on the boat. The children fled in terror to the other side of the boat, which then capsized, and many of them were drowned.

The teacher having anticipated trouble because of homosexuality, the rocking boat fantasy clearly conceals the fear of complete ruination if something is not done about his sexual situation. It is not the children but he himself who has to behave well, and apparently it takes a strong effort to do so. The desire to yield is stronger, so the fear of ruination had to fade into a mere fantasy.

PROBLEMS OF DREAM CONSTRUCTION

Dreaming that We Dreamed This Before. Structural manipulation of the inner dream may result in a shift and place the inner dream in an antecedent relationship to the outer dream in order to confuse the issue of reality. The attempt at such persuasion, however, does not succeed and cannot succeed, though it may be difficult to bring the painful memory to light. Here is an interesting example:

"I was in a room. The door to my left had a glass-paneled transom. Another door led into a brightly lit room, but stood at such an angle that I could not see the contents of that room. Suddenly, I saw two men trying to break in from the corridor. They could not open the door. I sat in an armchair and relaxed. Then I saw my

brother Boris climbing in through the transom and open the door. I was very frightened and could not stop him. With the other man, whom I did not see, he started stealing my things. All at once, the feeling came over me that I had had this dream once before but I could not tell when and where. I knew the room. It was gay, with rather dim and agreeable lights from the side walls. The oak table was very massive; the armchair was also oak and carved. In the other room a choir of men was singing the most beautiful melodies. I called for help but they did not hear me. I rushed to the door that my brother had just opened and came into a very elegant salon, with tapestries, bronzes, and nice furniture. In the middle of the room stood a very devoted servant of my husband whom we always treated as a friend. 'Lina, won't you help me?' I asked. She laughed: 'How can I help you against your brother?' I went back and told my brother that he was ruining me, taking from me everything. Then again I went out and tried to call for help. Instead of the servant, a beautiful young woman in crinoline sat on a chair perfectly still and just looked at me."

This dream was brought to the fourth analytic session by an artist. It has the hallmark of a dream of assault. Her brother broke the glass in climbing in through the transom, which suggests sexual violence destroying her hymen. She was positive that no bleeding took place at the time of her first sexual surrender, but she had ridden horses all her life and had had plenty of falls. She may have lost her hymen any time during her life. The dream is not necessarily a record of actual facts. It may be a fantasy built on a lesser sexual intimacy, on the desire and fear of assault, even though the theft of all her precious possessions does indicate the loss of her innocence. She remembered that Boris used to kiss her breasts, which gave her her first sexual excitement, but she was emphatic that her brother had never touched her genitals. That statement is no stronger proof for the negative than the dream is for the positive. Boris was two and a half years older and he may have made a digital attack against her when she was too small to remember. Such an exploration of an infant's genitals is usually covered by infantile amnesia.

Boris was not alone in the attempted burglary. The presence of the other man might indicate that Boris made two attempts or that two people had made a sexual attempt against her. It is at this point that the sensation is experienced in the dream that all this had happened once before. Therefore, a third query may also be raised: Was the dream of assault involving brother Boris a fantasy built on the forgotten memory of a real assault? The oak table and armchair were from the parental home but the lighting was more modern. The original lamp appeared in her birth dreams. Pursued by wolves, she floated up to the lamp and found refuge. These dreams appeared to symbolize an escape from the trauma of birth back into the prenatal state, the lamp standing for the maternal genitals and the floating for the uterine sensation of peace. If, then, the lamp is more modern, does that indicate a later period? If so, how late?

Boris may easily have represented someone else. Not only do we hear two men mentioned, but also two doors, two rooms, two women, and two periods. Presently, the patient's trail of association led to a grandfather whose name was also Boris and whom the brother resembled slightly. This grandfather died at the age of 97

when the patient was 7 years old. Then the memory of the other, the maternal, grandfather came up. He died when the patient was 1 year old.

"Yet, I can see his face in front of me as if I had always seen him. He was a doctor, and my mother, who had a very strong father fixation, had her children delivered by him. He delivered me, too, at his own house. All my childhood I suffered from nightmares in which somebody looked in through a window and stretched out a hand to take me. I saw the hand slowly opening. Finally, I discovered that the hand was the doctor's who delivered me. It may not have been grandfather's. He had another doctor assisting him."

Is this nightmare memory and the obstetrician's hand a cover for digital exploration? Emphasis has been placed on the fingers. The window through which they reached in strongly suggests her genitals, her helplessness pointing to an infantile condition and the beautiful melodies in the other room hinting at the excitement that the exploration may have caused.

The patient did not stay long enough in analysis to permit the discovery of the true situation. Her requests for help do indicate the desire to annul something that had actually happened. In that sense the outer dream serves the purpose of release, but without a measure of success.

The Inner Dream Becomes the Outer Dream. This is another form of structural manipulation.

During the course of analytic therapy, the libido invested in the inner dream will be gradually withdrawn. In the course of it, the inner dream may be sufficiently catharized to become an outer dream, indicating progress. Here is a fascinating dream by an alcoholic patient to illustrate the process:

"I wake up and get up in the dream. There is a bureau next to my bed and next to the bureau is a wastepaper basket. (In reality, the wastepaper basket is at the other bureau.) I open the drawer to get dressed and put on a shirt. Then I get sick and start vomiting water. First I catch it in my hands. I might vomit over the shirt because the drawer is open. I debate with myself: here is the wastepaper basket; no, I'd better run into the bathroom. I do that. It seems mother is in the kitchen eating lunch. I put on a shirt and go into the kitchen, talk to her, and note that I had put on one of my dress shirts. So I go back to the bedroom to take it off and put on a real shirt. But on my way out I stop in the living room, and I am almost picked up by somebody from behind who places his hand around my solar plexus. I double up and vomit more water on my own bed."

The first thing to be noted is that he wakes up in the dream, which means he wakes up from an inner dream of unknown content. Actually, he revealed this unknown content in his prefatory summary of the night:

"I had a number of dreams in which I was paralyzed. I don't remember them. The paralyzed feeling was all over my arms. In one of them I came to you about it and said: 'My arms are paralyzed, absolutely weak.' You sort of smiled and pointed at my penis, saying: 'I wish it was that other thing.' "

Now we know why he is waking up. He is trying to get away from paralysis. That this is due to sexual fantasies is clear from the statement he ascribed to the analyst. It means: if the penis were paralyzed, the arm paralysis would pass.

In the light of this clue we can understand his mistake in putting on a stiff dress shirt when he goes to mother in the kitchen. It is a hint that his paralysis originates from the mother situation. This assumption is considerably strengthened by the fact that the dream was dreamed while the patient was lying on his mother's bed, instead of his own. This may suggest two things: that he is on top of mother, in which case the paralysis serves the purpose of inhibiting, or punishing for, an incestuous design, or that he is within mother's body (the bed) in the fetal situation. The two bureaus and the later "doubling up" may indicate that the dream moves, simultaneously, on both levels, merging the inner and outer dreams for the purpose of showing that the incest situation is the postnatal outcome of prenatal motivation. The change in the position of the wastepaper basket hints at the movement of libido and at catharizing wasteful neurotic emotions.

In order to understand the vomiting of water episode, it should be stated that although he was a chronic alcoholic, the patient did not drink beer. However, in a previous dream, he drank it obsessively and was worried that he had not left enough for his professor of gynecology. By associating the beer with urine and fetal waters, the patient furnished a clue to his vomiting in the present dream and also to his drinking compulsion. What he vomited was no longer beer but waste water, the well of desire for the repossession of the maternal body, and he ran into the bathroom to drain it. His dream life revealed frequent pregnancy fantasies and desires to be a woman. By drinking a lot he would have a bellyful and grow big in the stomach. The man who picked him up from behind was the analyst. He forced the water out of his stomach and made him vomit more, this time on his own bed instead of his mother's.

The dream is valuable as depicting the dynamics by which the unconscious attempts to help the patient's insight. The beginnings of the dream is almost a command: wake up and get rid of all this neurotic nonsense. If he succeeds, the need for an inner dream will be disposed of.

DÉJÀ VU

The sensation in dreams that this has happened before closely parallels the waking experience called déjà vu. It is associated with both places and events. It inspires the mystic-minded to think of memories of a previous existence, a theme that has been exploited by novelists time and again. It has many variations but no completely satisfactory explanation.

The simplest approach to the problem is an experimental one. Look around at the many strange faces that surround you in a subway car. You make quite sure that none of them is familiar to you. Then turn away, do something else, and look back again. Now the faces look familiar and occasionally you begin to doubt whether the familiarity is due to a recent impression or dates from the past. It is the interposed mental preoccupation that is responsible for the false recognition.

Hence, the first consideration in the critical examination of the déjà vu is the question: is the experience a recent one retrojected into the past? As "experience," however, we should not include factual matters only. A fantasy, a dream, or a

daydream may also be subject to retrojection and false recognition, provided some dramatic association gives it a startle reaction. Freud ascribed the déjà vu to unconscious fantasies suddenly recovered and displaced.[3] Ferenczi attributed them to a forgotten dream or daydream from the night before. However, none of these theories account sufficiently for the drama of the experience. If the déjà vu is solely due to the causes mentioned, why don't we have it reported more frequently? The very rarity of the experience suggests that the problem is an unusual one. A curious depersonalization accompanies the experience. Reality becomes peculiar and vague and there is an accompanying feeling of fatality. The percipient feels that something inevitable has caught up with him and he displays awe, intense excitement, or wonderment. There is also a feeling of positivity. The experience is real, more real than reality itself. What then could account for it?

Stekel was the first to observe that womb fantasies have the curious appearance of the déjà vu, or the contrary, i.e., that something, a street for example, looks strange and new.[4] I have also elaborated on this.[5] Hence, any place, real or dreamed, that stimulates or symbolizes prenatal memories could give rise to the experience of déjà vu.

Here is a simple dream: "A Roman Catholic Church is located near me. I decide to go inside. It seems as if I had been there before in another dream."

The other dream, the inner dream, is a reference to prenatal life, of which the Church is a universal symbol. Whether that reference is made for reason of pain or pleasure is another question. So far we have assumed that the inner dream conceals unbearable pain and the purpose of this particular dream construction is to wish away that pain. But it is just possible that in some inner dreams not the pain but the form of the dream, the situation it depicts, is the important thing. While it is likely that the prenatal setting is used for the purpose of revealing traumatic emotions, it is also possible that the setting is used for consolation by way of retrojection. That, in a way, is also a wishing away, but it may be aimed at the content of the outer dream and not the inner one.

Past or Future. This is an upsetting possibility and it warns us to go carefully and not be too emphatic in fitting inner dreams into a preconceived framework. It is also conceivable that the recognition involved in déjà vu is false because it appears to cover the past instead of the future. The vision, fantasy, or daydream may have been premonitive at the time of its occurrence, but the ignorance of its nature made its proper evaluation impossible until fulfillment in reality. A man told me that during the war he was handcuffed as a prisoner of war. In a flash, it came back to him that he had dreamed the same scene four years before, but he did not recall the dream until the event actually happened. This, of course, may also be false recognition or just pure coincidence, but it illustrates the point. In its wake appears the thought that if a dream can be of premonitory character and it acquaints us with something painful that is as yet to happen, its purpose as an inner dream is the same as if it referred to the past: to make a future pain instead of a past one unreal and save the ego from gloom. If the inner dream can refer to the fetal past in which chronologic time is replaced by the biologic time of growth, it may perhaps transcend reality when it touches on the limbo of the future. The question is a clinical one.

If premonitory or prophetic dreams are admitted as ever having occurred in the lifetime of any individual, the question should not be ignored whether the content of the inner dream could or could not be perception of the dangerous future, however incomprehensible the process of such mental activity may be.

The dream of Penelope about the killing of the suitors may be an appropriate illustration. An eagle swooped down on her geese and killed them. Then the eagle spoke to her and said: "This is no dream, but a vision of good omen that surely shall come to pass. The geese are the suitors, and I am no longer an eagle but your husband, who am come back to you, and who will bring these suitors to a disgraceful end."[6]

Here the statement, "this is no dream," represents the outer dream in which the unbearable conflict with the suitors is resolved. Penelope has decided that the suitors must be killed and uses her husband for legitimation of the wish to kill. At the same time, the dream appears to reveal a prophetic element, for the beggar to whom she told the dream was Odysseus returned, and presently he did kill the suitors, as Penelope had wished. If the dramatic tension of wishes has a shaping effect on the future, this story is also an illustration that what we foresee is of our own making; hence a total knowledge of the content of the unconscious possibly might enable us to understand the future in the same manner as we can understand the past. Against this optimistic interpretation, however, stand some weighty criminologic considerations. By telling her dream to the old beggar, Penelope was actually abetting Odysseus to murder. She may have, unconsciously, penetrated his disguise but kept this withheld from her consciousness, in order to protect her innocence. The omen, as her dream claimed to be, was a sign of the participation of the gods in human affairs. How could Odysseus avoid this trap and refrain from accomplishing that which was rendered to him through his wife's dream as a compulsive divine reality? Hence, it is possible to argue that Penelope's dream was not a shadow cast by the future but the design of a murderess to whose clever scheming Odysseus fell a ready victim.

BIBLIOGRAPHY

1. Freud, S.: Interpretation of Dreams, London, George Allen and Co., 1920, p. 313.
2. Gutheil, E. A.: Language of a Dream, New York, Macmillan Co., 1939, p. 193.
3. Freud, S.: Psychopathology of Everyday Life, London, T. F. Unwin, 1920, p. 320.
4. Stekel, W.: Sexual Aberrations, New York, H. Liveright, 1930, p. 149.
5. Fodor, N.: Fantasies of Prenatal Bliss in the Search for the Beloved, New York, Hermitage Press, 1949, pp. 208–213.
6. Homer: The Odyssey of Homer, New York, Walter J. Black, 1944, p. 248.

MEDICAL INSTRUMENTS SECTION*

Modern Cancer Cell Screening Technique

H. E. Nieburgs, M.D.

NEW YORK, N. Y.

The diagnosis of cancer is usually made when the symptoms are indicative of an advanced lesion. Carcinoma in its early stage of development is usually asymptomatic and can be detected only if tests are made routinely as a cancer control measure. Numerous cytologic procedures are now available for the routine detection of early cancer, and inaccessible regions of the body can be reached for the collection of cellular material. Through the use of the endocervical smear method, the diagnosis of cervical carcinoma is now possible at an early stage. Routine application of the method to all patients, regardless of symptoms, has brought to light carcinoma in situ lesions that are asymptomatic in more than 80 per cent of cases. General population screening projects carried out in Floyd County, Georgia,[1] and Shelby County, Tennessee,[2] resulted in the diagnosis of a large number of cases of unsuspected carcinoma in situ.

There is growing evidence that mass screening of the entire female population may eliminate death from cervical carcinoma by its diagnosis in the curable in situ phase. The cytologic technique is now also undergoing an extensive trial for the detection of early carcinoma of the stomach.† It is anticipated that cytologic examinations carried out at periodic intervals in patients with gastric achlorhydria and hypochlorhydria may reveal early and possibly curable malignant gastric lesions.

The implementation of cancer control projects requires a large number of trained technicians. The wider acceptance of the cytologic method for cancer detection and diagnosis has considerably increased the number of cytologic specimens in most laboratories, while there is a great shortage of adequately trained technicians for the preliminary screening of slides.

The microscopic examination of cytologic specimens is a laborious and time-consuming procedure. Technicians trained to screen slides taken routinely for cancer detection are usually unable to examine more than 25 to 30 slides per day after at least 6 to 12 months of training. In addition, it is not always certain that an adequate area of the slide has been examined. Often cells seen through the microscope have to be described individually to each technician. The recognition of cancer cells, although based on definite criteria, must be taught mainly by practice through repeated microscopic examination. Morphologic studies of cells in regard to size,

* The Medical Instruments Section will be featured in this journal during 1957. Outstanding authors have contributed articles to this series that will depict a panorama of the role of scientific instruments in clinical medicine.

† Cancer Control Project, New York City Department of Health, Division of Cancer Control and Research.

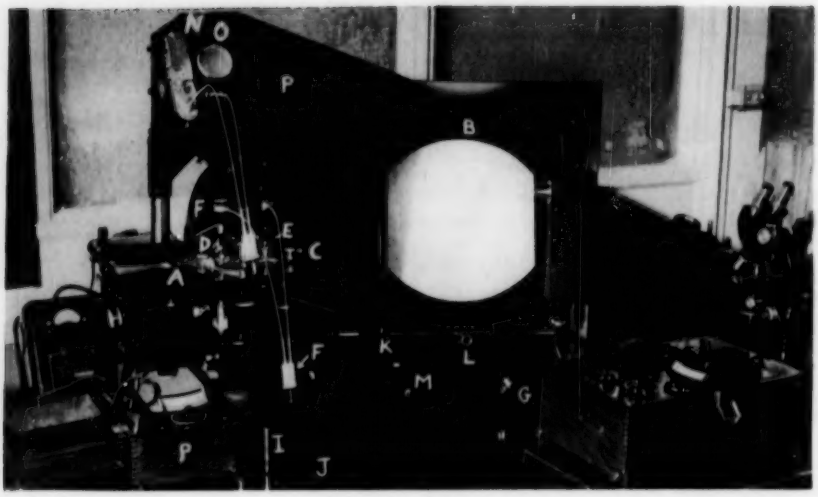


FIG. 1. Cyto-viewer. *A:* Motor-driven stage. *B:* Translucent screen. *C:* Knob for adjustment of cover slip location. *D:* Adjustment for size of cover slip. *E:* Adjustment for size of area to be scanned. *F:* Slide-marking device. *G:* Focusing adjustment. *H:* Focusing adjustment. *I:* Control of movement of mechanical stage and direction of movement. *J:* Control of speed of movement. *K:* Crossline. *L:* Knob connected to crossline. *M:* Micrometer scale. *N:* Camera. *O:* Ground glass screen. *P:* Photoelectric cell.

changes in nuclear chromatin, and density are not simple with microscopes used for routine examinations. In order to solve these problems a microscope called the Cyto-viewer was designed and built in cooperation with E. Leitz, Inc., which enables the scanning of a large number of slides, increases the accuracy of detection, facilitates the training of technicians, and allows the study of cellular morphology by instruments attached to the microscope and is easily operated even during routine scanning. Thus the Cyto-viewer has been produced for the purposes of scanning, research, and teaching.

To facilitate the scanning of cytologic specimens, the mechanical stage (fig. 1, *A*) is motor-driven and moves automatically to cover any desired area of the slide. The image appears on a translucent screen (fig. 1, *B*) at a magnification of 400, 800, 1600, or 2000. It is equipped with instruments that allow adjustment in accordance with the location of the cover slip on the slides (fig. 1, *C*), the length of the area to be examined (fig. 1, *D*), and the number of and distance between each longitudinal run (fig. 1, *E*). Furthermore, a slide-marking device (fig. 1, *F* and fig. 2, *A,B,D*) has been incorporated in the microscope that allows marking of the slide by pushing a cable release. An additional synchronized instrument can be fitted to another microscope, enabling placement of the noted cells directly under the objective by a simple lever movement (fig. 2, *C*). The ink dot made by the pen (fig. 2, *B*) of the slide marker is focused under the objective. When lever *C* (fig. 2) is pushed until resistance is encountered, the marked cell appears in the center of the objective. The cell or cell group marked by the device (fig. 2, *A,B,D*) may also be identified by

FIG. 2. Slide-marking device and automatic cell finder. *A:* Holder for marking pens. *B:* Marking pen. *C:* Lever for automatic location of marked cells. *D:* Cable release for slide marking.

simply placing the ink dot on either the right or the left point (fig. 3, *i*) permanently made on the stage at a distance from the center of the objective equal to the length of the slide-marking pens (fig. 2, *B*). Two focusing adjustments can be used: one in front of the screen (fig. 1, *G*) and one to the left of the microscope (fig. 1, *H*). A single lever (fig. 1, *I*) is provided either to stop the mechanism or to change the movement of the slide in either direction. The speed of the movement can be adjusted to low speeds imperceptible to the eye for higher magnifications (fig. 1, *J*). The advantages of these features are: increased speed of examination, decreased fatigue, and increased accuracy of diagnosis.

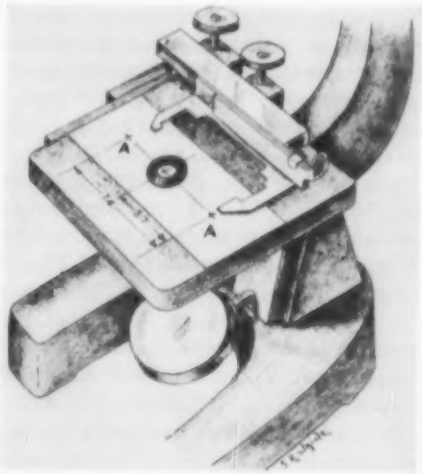


FIG. 3. Synchronized stage for location of marked cells.

FIG. 4. Cyto-viewer in operation.

Two light sources are provided for the microscope: a low voltage incandescent lamp for photomicrography and a high intensity mercury vapor lamp for scanning.

In order to facilitate morphologic studies of cells, the screen has been equipped with a micrometer. (fig. 1, *K*, *L*, *M*). This is operated by moving a crossline (fig. 1, *K*) to any part of the screen by turning a knob (fig. 1, *L*). The diameter of the cell component that is being measured appears on the lighted scale (fig. 1, *M*). At the magnification of 400, 1 mm. is equal to 2 μ. Cell density measurements are carried out with the Photovolt Electronic Photometer, model 514, which has been designed for the measurement of very low light values. It shows full scale deflection at approximately 0.005 foot-candle. It is provided with a scale for light transmission and density. Furthermore, the microscope has been fitted with a camera attachment (fig. 1, *N*) for photomicrography, which is synchronized with the screen. The image may also be focused on the ground glass attachment (fig. 1, *O*). A built-in exposure meter (fig. 1, *P*) using the Photovolt Universal Photometer permits quick determination of the exposure time or amount of light used.

The teaching of cytology is greatly facilitated by the use of the translucent screen, which permits demonstration of cell types to a large group of students. The difference between normal and malignant cells can be more easily demonstrated by cell measurements, nuclear chromatin changes, and density determinations.

This microscope has been tested by the scanning of specimens obtained from 100 patients with known cervical lesions with 100 per cent accuracy. It was found that

not more than an area of 52 square mm. had to be examined in order to maintain 100 per cent accuracy. This can be carried out in 2 minutes, 10 seconds, to 2 minutes, 25 seconds, with an average time of 3 minutes/slide, which includes feeding of the microscope and reporting by the use of a dictating machine. The Cyto-viewer has been used for the scanning of several thousand cases and for teaching a large group of technicians. An average of 125 slides can be examined daily by each technician with this microscope.

It is suggested that the use of the Cyto-viewer may allow the screening of the general population for cervical cancer as well as for cancer in other sites of the body at a considerably lower cost than was hitherto possible. Furthermore, it is anticipated that measurements of size of cells, nucleus, and chromatin particles and density determinations may establish more definite scientific criteria for the differential diagnosis between benign and malignant cellular changes.

BIBLIOGRAPHY

1. Nieburgs, H. E.: Mass screening of the total female population of a county, J. A. M. A. In press.
2. Erickson, C. C.; Everett, B. E., Jr.; Graves, L. M.; Kaiser, R. F.; Malmgren, R. A.; Rube, I.; Schreier, P. C.; Cutler, S. J., and Sprunt, D. H.: Population screening for uterine cancer by vaginal cytology: preliminary summary of results of first examination of 108,000 women and second testing of 33,000 women, J. A. M. A. *162*:167, 1956.

Dr. Co Tui Invited by President of Philippines to Conduct Medical Survey

Co Tui, M.D., Associate Research Scientist at Creedmoor Institute for Psychobiologic Studies in Queens Village, New York, has been honored with an invitation from President Magsaysay of the Philippine Islands to conduct a broad survey on all scientific needs and development in that country. He will spend six weeks there on this project and then tour Europe before returning to Creedmoor.

Dr. Co Tui has been engaged in medical research since 1929. From 1932 through 1949 he was Associate Professor of Experimental Surgery at New York University College of Medicine. In 1937 he founded the American Bureau for Medical Aid to China and was decorated by its republican government; he headed a special medical mission to China in 1946. He joined the staff of Creedmoor in 1949 as Director of Biologic Research.

Dr. Co Tui is a member of the New York Academy of Medicine and of the Society for Experimental Biology and Medicine as well as of other professional organizations. He is also Honorary President of the International Anesthesia Research Society.

He has made numerous contributions to medical journals, including the Journal of Clinical and Experimental Psychopathology.

At present, he is interested in adrenocortical function and the ataractic drugs. Psychiatric patients from Creedmoor and from other hospitals are the subjects of his studies.

Humpty Dumpty on Writing

In these days of hurly-burly it is perhaps not unseasonable to consult Humpty Dumpty on the art of using words to communicate events or thoughts.* That foolish character was in many philologic respects in advance of his time, and in the practice of manipulating words to suit his immediate purposes he could estimably serve as an example.

His first demonstration of advanced communication is when he uses the term "there's glory for you." Alice timidly inquires what the word "glory" means, and receives Humpty Dumpty's definition that it stands for "there's a nice knock-down argument for you." Quite justifiably, Alice protests that "glory" means no such thing, to which he scornfully replies: "When *I* use a word, it means just what I choose it to mean—neither more nor less."

This is a classic utterance, on a par with Descartes' *cogito ergo sum*, and Louis XIV's, "*l'état, c'est moi.*" It requires no scientific demonstration, no tiresome juggling with Scholastic rules of logic; it is a manifesto of supreme individualism and what the older German school of psychologists might call *Selbstvertrauenswillen*. It is, by the way, entirely in harmony with the attitude of too many contemporary medical writers for whom the English language is a mere instrument of self expression, unrelated to customary rules of grammar or of modern usage.

For example, when an author writes: "Physical modalities called for in the management of the cutaneous disorders are chiefly those adaptable to superficial application," he is quite obviously a devoted "Humpty Dumptarian." He makes a string of undeniably English words perform in *his* manner and not in the manner of Fowler or Fishbein. He sets himself up as the *Ursprung* of grammar and syntax and tries to soar above the trivialities of man-made rules. As Humpty Dumpty proudly replies when Alice asks whether anyone can make words mean so many different things: "The question is, which is to be master—that's all."

This question must haunt many physicians when they first face a blank page of paper. Their brief study of English grammar in public school is long behind them, and since then their daily encounter with professional language has been largely confined to tongue-twisting medical terms compounded mostly of Greek and Latin.

But to return to Humpty Dumpty. His *coup de maître* is surely delivered when Alice, in all innocence, asks him what the word "impenetrability" means. He replies benignly: "I meant by 'impenetrability' that we've had enough of that subject, and it would be just as well if you'd mention what you mean to do next, as I suppose you don't mean to stop here all the rest of your life."

What a masterly definition of that one word. How often it shadows the mind of the medical editor when faced with an impenetrable sentence. What, he asks himself in despair, does the author mean to say next? Will enlightenment dawn in

* Carroll, L.: Through the Looking Glass, 1871.

the next paragraph, or will the reader remain puzzled? Will the summary contain the essence of the whole thesis, as it mercifully often does in a medical article, or will it trail off into telegraphic platitudes?

We should note that when Lewis Carroll presented the world with a poem containing truly nonsensical words such as the Jabberwocky, he reserved for Humpty Dumpty the essential task of explaining to Alice such words as "brillig" and "borogroves." The definitions may appear to be nonsensical also, but at least they are definitions, whereas the authors of bad medical writing afford us no such consolation; they use words in their own fashion and leave us to define what was originally intended.

This may be delightfully innocent, and in fact almost inevitable, in an abstruse work on philosophy, but it should have no place in medical writing. A physician either knows what he means and says what he knows, or he is a mere obscurantist better fitted for a medieval disputation than for a twentieth century clinic. In this era, when words can be electronically transmitted around the earth's belt in a fraction of a second, the words must be concise and crystal-clear.

The outlook is not all bleak. The fact that more and more attention is being paid in both American and British medical schools to the art of medical communication is a good portent. The added fact that several leading medical journals, including this one,* have devoted articles and symposia to the subject of better medical writing is an encouraging signpost to the future. We must hope that the autocratic way of Humpty Dumpty with words will never become standard usage in medicine.

---

* Symposium on Medical Writing, Internat. Rec. Med. & G. P. C. *168*:609-675 (Oct.) 1955; Symposium on Medicine and Writing, Internat. Rec. Med. & G. P. C. *169*:685-750 (Nov.) 1956.

Carl Gustav Jung on "The Mind of Man"

Dr. Carl Gustav Jung, participating in the Voice of America's continuing international symposium on "The Frontiers of Knowledge and Humanity's Hopes for the Future," stated that, inasmuch as no psychologically understandable agent has ever been discovered to cause schizophrenia, he now concludes that the illness might have a toxic cause due to an "organic and local breakdown." He stated that physiologic changes take place because the brain cells are subjected to emotional stress beyond their capacity and that experiments with mescaline and related drugs encourage the theory that symptoms of schizophrenia are toxic in origin.

The search for the specific toxin is the task for clinical psychiatry, stated Dr. Jung. And for the psychopathologist and psychiatrist the task ahead is to study the delusions of schizophrenia and their meaning, for "beyond the personally acquired contents of the personal subconscious mind of each of us, there is a deeper stratum—a stratum of the collective unconscious mind of the human race." Research into the problem of the human mind *in toto* is new, but, states Dr. Jung, we now have a real opportunity for increasing our understanding.

BOOK REVIEWS

Handbook of Biological Data. Edited by WILLIAM S. SPECTOR. Philadelphia, W. B. Saunders Company, 1956.

This handbook represents the combined efforts of more than 4000 contributors, condensed into tables of standard data. More than 20,000 sheets of data were statistically proportioned into various groups for presentation in tabular form. All integrated data were verified and authenticated prior to publication. A wide range of scientific subjects is embodied, including: biophysical characteristics; genetics, cytogenesis, and reproduction; development; nutrition and metabolism; respiration and circulation; physiologic performance; biologic active compounds; environment and survival; symbiosis and parasitism; ecology and biogeography. The format of the book is remarkably clear and concise, the data useful and accessible, and the book as a whole invaluable as a ready source of reference.—*I. Newton Kugelmass, M.D.*

Physician's Handbook, Ninth Edition. MARCUS A. KRUPP, NORMAL J. SWEET, ERNEST JAWETZ, AND CHARLES D. ARMSTRONG. Lange Medical Publications, 1956. Price $3.00.

This handbook offers a readily available source of first hand data on laboratory procedures and is a clinical aid in all branches of medicine. There are brief discussions of fundamental sciences involved in everyday practice. The book is intended primarily for the medical student but is invaluable for the practicing physician as an up-to-date summary of the principles and practice of medicine. The book is unique in that it elaborates on the examination of the heart, preparation for roentgen-ray examinations, medical parasitology, medical mycology, hematology and blood chemistry, liver function tests, endocrine functions and tests, spinal fluid examination, radioisotopes, biologic products for prophylaxis and therapy, and drugs and hormones.—*I. Newton Kugelmass, M.D.*

Medical Parasitology, Second Edition. WILLIAM G. SAWITZ, M.D. Philadelphia, The Blakiston Company, 1956.

This handbook provides the essentials for the evaluation of parasitic disorders. After a classification of the parasite there is a summary discussion of Protozoa, helminths, and Arthropoda. The standard techniques for laboratory diagnosis are given as well as a vocabulary of technical terms. The book is an invaluable guide to tropical diseases.—*I. Newton Kugelmass, M.D.*

The Office Assistant in Medical or Dental Practice. PORTIA M. FREDERICK AND CAROL TOWNER. Philadelphia, W. B. Saunders Company, 1956.

This book presents the role of the office assistant in medical and dental practice. A wide range of topics is discussed in a stimulating manner, including: a career as

an office assistant, medical ethics and medicolegal affairs, the right kind of reception, telephone technique, appointments, handling the mail, medical and dental records, filing of records, medical and dental fees, extending credit and making payment arrangements, billing and collecting procedures, bookkeeping and banking.

—*I. Newton Kugelmass, M.D.*

Today's Industrial Nurse and Her Job. ERNA BARSCHAK, PH.D. New York, G. P. Putnam's Sons, 1956. Price $3.20.

This study is limited not only in its geographic area but also in its scope of the possible situations available for industrial nurses. The author merely tells what it means to a nurse to work alone and what it means to her when there are other members of a health team working with her. Considerable effort was expended in the accumulation of data on the nature of the nursing function in industry, but few conclusions are drawn worthy of the endeavor.—*I. Newton Kugelmass, M.D.*

Administrative Medicine, Transactions of the Fourth Conference, October 31, November 1 and 2, 1955, Princeton, N. J. Edited by GEORGE S. STEVENSON, M.D. New York, Josiah Macy, Jr., Foundation, 1956.

These round-table discussions of vital topics in administrative medicine include: "Measuring Needs for Medical and Related Services," "Health Insurance Plan of Greater New York," "Assessment of Quality of Services in a Group Practice Prepayment Plan," "Assessing Effectiveness of Program in Operation," "A Study of the Quality of Medical Care," "Assessment of Quality of Services in the Boston Metropolitan area," and "British Experience in Appraising Adequacy of Medical Care." These provocative discussions bring to light the newer objectives in institutional administration.—*I. Newton Kugelmass, M.D.*

The Merck Manual, New Ninth Edition. Edited by CHARLES E. LYGHT, M.D., WILLIAM P. BOGER, M.D., GEORGE A. CARDEN, M.D., AUGUSTUS GIBSON, M.D., AND DICKINSON W. RICHARDS, M.D. Rahway, N. J., Merck & Company, 1956.

The new edition of the *Merck Manual* of diagnosis and therapy has been prepared by more than 100 leading clinicians in the United States, Canada, and abroad. It offers the latest and currently accepted medical information, in 20 main sections, each thumb-indexed, covering specific fields of practice. There are about 1500 prescriptions embodying the most up-to-date medicinal advances; special procedures described include bedside, clinical, preoperative, postoperative, and office laboratory. Diagnosis and therapy are given primary emphasis, but pertinent physiologic, pathologic, and etiologic features are included. Up-to-the-minute coverage has been given to adrenocortical and related therapy, "tranquilizing" drugs, and antituberculosis compounds, as well as to agammaglobulinemia, kwashiorkor, and mucoviscidosis. Discussions of modern advances in the fields of antibiotics, nutrition, immunization, Rh factor, gamma globulin, and prenatal and postnatal care are extensive and bring together currently accepted developments on these subjects.

A wealth of readily applicable advice is set forth on such vital subjects as medical emergencies, burns, poisoning, and shock. Inclusion of reference values and conversion data, in addition to an index that is liberally cross-titled and substantially expanded over previous editions, makes the volume virtually indispensable to the physician and his associates in related fields.—*I. Newton Kugelmass, M.D.*

Principles of Clinical Electrocardiography. MERVIN J. GOLDMAN, M.D. Lange Medical Publications, 1956. Price $4.50.

The author presents the basic concepts of electrocardiography and their clinical application. He realizes that material so presented must be simplified and that an exhaustive and detailed treatment of the subject matter to be covered will not be possible. Emphasis has been placed on the unipolar leads. To one who first learned electrocardiography by memorizing patterns in the bipolar standard leads and later followed the development of unipolar electrocardiography, the latter offers a more logical approach to the subject material. The unitarian concept of the atrial arrhythmias and the theory of accelerated conduction are admittedly not universally accepted. However the author feels that these are the most acceptable theories of the phenomena available at the present time. The author cannot emphasize too strongly the fact that the electrocardiogram is a laboratory test only. Like all laboratory findings, an abnormal electrocardiographic tracing is significant only when interpreted in the light of clinical findings. Ideally, the person best qualified to interpret the electrocardiogram is the physician caring for the patient.

—*I. Newton Kugelmass, M.D.*

Handbook of Medical Treatment. Edited by MILTON J. CHATTON, M.D., SHELDON MARGEN, M.D., AND HENRY BRAINERD, M.D. Lange Medical Publications, 1956.

This handbook should fill a need of the medical student and practitioner. When the diagnosis is established, the clinician's first thoughts are for the welfare of the patient and to bring to bear the most effective therapeutic procedures at the earliest possible moment. He wants to know what to do first and how to use chemical and other effective methods in order to restore the normal physiologic balance and relieve symptoms, remembering always that symptoms arise from a disturbance of some normal physiologic mechanism. This collection of therapeutic procedures has been well received by students and practitioners. The book has become a necessity to the physician on the firing line of medical practice.—*I. Newton Kugelmass, M.D.*

DIVORCED WOMEN SUFFER MOST FROM ARTHRITIS. Although it has long been known that arthritis strikes more women than men, a new study shows that prevalence of the disease increases in women after they get married and is even higher for divorced women, reported Dr. Sidney Cobb, University of Pittsburgh. These findings were based on a study of 80,000 persons in the Arsenal Health District of Pittsburgh.

HOSPITALS TOO NOISY FOR GOOD HEART DIAGNOSIS. Faint heart murmurs that may be early signs of serious heart disease are going unnoticed in noisy hospitals, reported Dr. Dale Groom, Medical College of South Carolina. In an experiment to see just how noisy a modern hospital is, Dr. Groom found that the noise level in the clinic examining rooms ranged as high as from 72 to 75 decibels; the noise level inside a DC-6 airliner is 105 decibels.

SOCIAL IMPLICATIONS OF ATARAXICS. Research in the social implications of ataractic drugs, such as meprobamate, reserpine, and chlorpromazine, is now a major part of pharmaceutical company research programs, reported Dr. James G. Miller, director of the Mental Health Research Institute of the University of Michigan. Some of the problems being studied are: What will ataraxics do to initiative? Will they have any effect on a person's desire to work? Will a person's drive be lost?

PANEL STUDIES TREATMENT OF RHEUMATOID ARTHRITIS. Acetylsalicylic acid and salicylates continue to be "the most important drugs for acute episodes" of rheumatoid arthritis, in relieving pain, stiffness, and soreness, regardless of their cause, reported a panel of experts in a recent issue of the Ohio State Medical Journal. They agreed that these drugs are "effective, harmless, cheap, and available" and cited a recent British Nuffield Foundation study showing that acetylsalicylic acid proved as effective as cortisone in treatment of rheumatoid arthritis.

NEW DRUGS MAY CONTROL GLAUCOMA. A variety of new drugs, including ataractic agents, are now being used experimentally for glaucoma, reported Dr. Irving Leopold, University of Pennsylvania. Although administration of miotic eyedrops remains the basic treatment of this disease,

chlorpromazine, reserpine, and alkaloids of Rauwolfia serpentina are being experimented with, and it is predicted that some day they and other drugs may result in more effective control of glaucoma. Use of the ataractic agents is being explored "because of the profound influence of emotion on intraocular pressure."

TUBERCULOSIS RATES. Tuberculosis in some parts of the country is infecting people at the rate of 1 per 100 population per year, reported Donald Trauger, National Tuberculosis Association. Although fewer people are dying of tuberculosis than in years past, more than 15,000 will die of it each year. In persons more than 65, one death is reported for every 2 cases.

STEEL HINGE FOR DAMAGED FINGER JOINTS. A stainless steel hinge, for badly damaged finger joints, that works without pain and improves the appearance of the injured hand is now in use. Good results in 10 cases were reported by Lt. Col. Earl W. Brannon, U. S. Air Force Hospital, Lackland Air Force Base, San Antonio. The device is designed to prevent the unwanted rotation and instability that are common faults of other types of finger joint replacements.

CITRUS CHEMICALS USED FOR COMMON COLD. Chemicals from citrus fruit peels, called flavenoids, combined with vitamin C, also found in citrus fruits, brought "definite, objective relief" from both mild and severe colds in various stages, reported Dr. W. L. Macon, Jr., in the Journal of Industrial Medicine and Surgery.

15,000 CASES OF ADVANCED SYPHILIS FOUND IN VETERANS. Fifteen thousand veterans of World War II are estimated to have neurosyphilis at the present time, according to a report in the Journal of Chronic Diseases. Between 1940 and 1946, 500,000 members of the Armed Forces acquired or were treated for syphilis. Veterans who were treated with penicillin G after it became available in 1947 show less spinal fluid evidence of neurosyphilis now than those who were treated with the older penicillin K in 1946.

NEW RAUWOLFIA DERIVATIVE MARKETED. Rescinnamine, an alkaloid derived from the root Rauwolfia serpentina, is being marketed for use in control of hypertension and as an ataractic agent by Pfizer Laboratories under the name Moderil. The drug has been reported to have a great advantage over older Rauwolfia derivatives in that it produces milder side reactions.

ADVANCED REPORTS FROM CURRENT MEDICAL MEETINGS

This section of the INTERNATIONAL RECORD OF MEDICINE features reports on papers delivered at current medical meetings in the United States and abroad.

Colloidal Factors in Plasma Gels

Omaha, Neb.—The clotting of the blood is one of the most important natural phenomena, and it is being studied from many points of view, report Herbert L. Davis and Nora L. Davis (University of Nebraska College of Medicine, Omaha). A complicated picture has been developed that depends on the cooperation of many factors, compounds, complexes, enzymes, activators, proteins, lipids, calcium, in a variety of reactions simultaneous or consecutive, with feed-back mechanisms, inhibitions, and lysins included. Hematologists have made important advances with these tools and tests, and their diagnoses and treatments are saving thousands of lives. Another approach is to study the blood clot as the most important *gel* in the world. The application of colloidal principles to the components of the normally circulating blood should lead to an understanding of the mechanisms by which this sol is converted to a gel (thrombus or clot) or fails to be so converted (bleeding and hemorrhage).

Plasma albumins and globulins determine the colloidal stability of the formed elements and the other plasma components in the blood. These proteins are stabilized by their natural charge and their bound water. Coagulants are positively charged (cationic) substances that reduce the charge, or they are dehydrating agents to displace or remove bound water. Anticoagulants are anionic substances to increase the negative charge, or they are hydrating agents to increase the over-all bound water of blood proteins. The fibrinogen-fibrin components are of maximum significance in gel formation by these mechanisms.

Citrated plasmas form gels when calcium chloride is added, and the rate of gelation is increased by ethanol. Intermediate amounts of calcium alone or of calcium plus ethanol produce gels in minimal time periods, but excess of calcium and/or ethanol retards and prevents gel formation. When this experiment is repeated with sodium oleate in place of the ethanol, a similar reaction is found—minimal gel time periods with intermediate amounts of calcium and of soap. Sodium stearate is more effective than the oleate in forming gels, and in some plasmas will do so without calcium addition. Several experiments along this line suggest a mechanism of gel formation independent of calcium but dependent on the lipids. The frequent observation of irregular series effects in such gel formations argues against many current concepts in blood coagulation. Lipid effects on colloidal stability of the blood appear relevant to fat embolism, arteriosclerosis, coronary infarcts, and similar abnormalities in blood flow.

(Presented before the American Association for the Advancement of Science, New York City, Dec. 26, 1956.)

Accidental Poisoning in Children

Chicago.—The most common types of substances involved in the accidental poisoning of children in Chicago from 1954 to 1956 were: medications, 50 per cent; cleaning agents, 20 per cent; pesticides, 10 per cent; petroleum distillates, 10 per cent; and others, 10 per cent, reports Joseph R. Christian (Chicago). The medication most frequently involved in such accidents was acetylsalicylic acid and in particular, flavored acetylsalicylic acid of the type often purchased for administration to children.

The central problem in coping with acci-

dental poisoning of children was felt to be making available reliable information concerning the toxic constituents of commonly used products, symptoms resulting from ingestion of such products, and suggested courses of treatment at the level of the treating physician.

Suggestions for limiting the problem included the elimination of pleasant flavoring in medicines, careful limitation of the amounts of medicine prescribed, wide educational efforts at the professional level, and the recognition of the problem as a state-wide public health concern.

(Presented before the Jackson Park Medical Society, Chicago, Nov. 15, 1956.)

Effects of Hormone Therapy in Aging Patients

New York.—Of 42 aging patients given a mixture of estrogens, androgens, and thyroid for three months, 74 per cent showed improvement in mental alertness, general well-being, and appetite, with a consistent trend toward improvement in scores on a memory scale test, reports Winnifred Seegers (New York Medical College). The results showed that in men, urinary 17-ketosteroid excretion was depressed. No consistent changes were seen in basal metabolism rate, protein-bound iodine, or cholesterol. Total protein and albumin showed a fairly consistent downward trend. Other laboratory findings were unchanged. Vaginal bleeding, breast tenderness, or increased facial hair growth occurred in some women.

(Presented before the Ninth Annual Scientific Meeting of the Gerontologic Society, Inc., Chicago, Nov. 8–10, 1956.)

Aging in the Atomic Age

Martinsburg, W. Va.—The three effects of excessive exposure to radiation are the genetic effect, premature aging, and the late cancerous effect, says A. F. Abt (Veterans Administration Center, Martinsburg). In discussing the medical applications of radioisotopes, he points out the differences in symptoms of hyperthyroidism in young and old patients. Geriatric patients, he says, may have a masked apathetic hyperthyroidism, and instead of showing the classic symptoms of nervousness and fatigue, they may show signs that seem to suggest heart trouble. The patients will have auricular fibrillation, rapid pulse, and congestive heart failure.

Dr. Abt says that radioisotopes may help in the study of the aging process, particularly the study of arteriosclerosis. A study of premature aging by ionizing radiation may throw light on the processes of aging and wound healing.

(Presented before the Ninth Annual Scientific Meeting of the Gerontologic Society, Inc., Chicago, Nov. 8–10, 1956.)

Hormone Therapy in Rheumatism

Oklahoma City.—A mixture of androgens, estrogens, and thyroid given to patients with rheumatism produced improvement in more than 80 per cent of the cases, reports W. K. Ishmael (University of Oklahoma School of Medicine, Oklahoma City). The percentage was slightly less without the thyroid. Almost 27 per cent showed improvement when given placebos. Dr. Ishmael says that this therapy was begun when it was noticed that many women began to complain of rheumatism after the menopause. Painful, degenerative changes in the muscular-skeletal structure are due to three principal factors: stress or the effects of wear and tear through the years, the personality of the patient, and the physiologic effects of aging, which reduce the ability to withstand stress. It is important, he says, to consider all three factors when determining if the complaints are of organic or of psychogenic origin.

(Presented before the Ninth Annual Scientific Meeting of the Gerontologic Society, Inc., Chicago, Nov. 8–10, 1956.)

Clinical Observations in Infectious Hepatitis

Pakrac, Yugoslavia.—From 1952 until the end of 1955 there were 407 patients hospitalized in the General Hospital, Medical De-

partment, Pakrac, because of infectious or homologous serum hepatitis, reports R. Zivkovic (General Hospital, Pakrac). The patients have been reviewed from different clinical aspects; 259 were controlled by clinical and laboratory tests in May and June, 1956.

The number of patients with hepatitis hospitalized during one year was on a constant rise. The disease occurred in small epidemics. The majority of patients were between 5 and 30 years of age. The incidence of hepatitis in the population was higher than in the literature reports from other countries. It was impossible to find any reliable clinical criterion for the differentiation between infectious and homologous serum hepatitis. Only the clinical history was of considerable help. Among young people there was a majority of "mild" forms and anicteric forms.

Ten per cent of patients had clinical or laboratory signs of liver disease three years or more after the onset of hepatitis, indicating that hepatitis is by no means an innocuous disease. The occurrence of hepatitis among the patients hospitalized for other reasons has fallen 80 per cent since the introduction of prophylactic measures.

(Presented before the Annual Medical Meeting of the Slovenian and Croatian Internists, Portoroz, Yugoslavia, Oct. 8–13, 1956.)

Development of Measles Vaccine

Boston.—"Investigations have provided tools whereby the (measles) virus can be readily isolated, its infectivity accurately determined, and its pathogenic, immunogenic, and other biologic properties analyzed," reports John F. Enders (Chief of Research Division, Children's Hospital, Boston).

He reveals that he has succeeded in propagating the virus in chick embryos. "From the more immediately practical standpoint, it is evident that methods of directly assaying the antibody content of different preparations of gamma globulin, or other materials used in the production of passive immunity, are already at hand," he declares. "It also seems," Dr. Enders continues, "that the groundwork has been established for future studies directed toward the development of vaccines, whether composed of attenuated or inactive virus. We are encouraged to believe that progress toward this objective was made when we succeeded in propagating the agent in chick embryos.

"In our opinion, virus grown under these conditions or in cultures of chick tissue would represent the most suitable material for the preparation of vaccine. For there is potential risk in employing cultures of primate cells for the production of vaccines composed of attenuated viruses, since the presence of other agents, possibly latent in primate tissue, cannot be definitely excluded by any known method. For the preparation of inactive virus vaccine, chick embryonic tissue would also appear to be advantageous. Not only would it afford relative assurance of the absence of extraneous viruses in the starting material, but it would also greatly reduce the cost of manufacture. Much investigation will, however, be necessary, since first it must be determined whether multiplication of the virus in chick tissue will continue indefinitely, whether sufficient viral antigen is produced under these circumstances to be immunogenic when inactivated, or whether attenuation of pathogenicity for monkey and man may occur as a result of passage in chick tissue," he says.

(Presented before the American Public Health Association Convention, Atlantic City, N. J., Nov. 12–16, 1956.)

Variables Affected by Drug Action

Brooklyn, N. Y.—A survey of the techniques that experimental psychologists use in the study of drug action and a description of the main variables affected by drug action are reported by Murray Jarvik (Albert Einstein Medical College, Brooklyn). These variables are: (1) Sensation, which is the most easily measured. (2) Movement and secretion, which have been studied by physi-

ologists as well as psychologists. Many indices are available for these. The tendency is to make these measurements more technical and electronic. (3) Motivation and emotion. These measurements are usually left to the psychologist and psychiatrist, and exact measurement is difficult. (4) Intellectual functions: (a) perception; (b) behavior or action; (c) learning; and (d) thinking. We are as yet unable to measure discrete intellect variables and must use the above rough classification, says Dr. Jarvik.

(Presented before the American Psychiatric Association Regional Research Conference on Research in Psychiatry, Philadelphia, Nov. 16–17, 1956.)

Report on BZ-55 and Orinase

Ann Arbor, Mich.—Insulin substitutes known as aryl sulfonylurea compounds have to go a long way before proving themselves, according to Stefan Fajans and John A. Moorehouse (University of Michigan, Ann Arbor). They report on extensive metabolic balance studies and the numerous individual testing procedures performed before, during, and after administration of two recently appearing compounds, BZ-55 and orinase. Study subjects included various types of persons from normal men to diabetics, to a completely depancreatized woman.

It was found that severe hypoglycemia was produced in the normal men after administration of the sulfonylurea compounds. Dr. Fajans states, ". . . in normal men and those diabetics who exhibit a blood sugar-lowering response to these compounds, we have demonstrated that under their influence there occurs: (1) no significant change in glucose tolerance tests; (2) persistence of hypoglycemia, induced by adrenalin and glucagon; (3) no consistent change in sensitivity to exogenous insulin; (4) no significant change in the urinary excretion of 17-hydroxycorticoids or 17-ketosteroids; (5) no direct or consistent effect on balances of nitrogen, sodium, potassium, and chloride; (6) no effect on prednisolone-induced loss of carbohydrate tolerance; (7) no alteration in the metabolic effects produced by prednisolone; and (8) no evidence of impairment of liver function."

The sulfonylurea compounds were found by Dr. Fajans to have no appreciable blood sugar-lowering effect on many diabetics. In these patients, he states, the compounds had no effect on insulin sensitivity as measured by insulin tolerance tests, nor was there any difference in insulin requirement indicated, whether the diabetes was controlled with insulin plus sulfonylurea compounds or insulin alone. Dr. Fajans states, "BZ-55 cannot be substituted for insulin in the pancreatomized human."

Whereas BZ-55 caused a "great depression of thyroidal uptake of I^{131}" in 1 patient, Dr. Fajans indicates that the administration of orinase resulted in a carbolic acid derivative of this compound being excreted in urine as a major excretory product. He adds, however, that this compound exerts no hypoglycemic effect. Dr. Fajans found that the blood sugar-lowering properties of sulfonylurea compounds are not a result of potentiation of insulin activity, as no evidence of this could be demonstrated.

The data he presents do indicate, however, that sulfonylurea compounds "(1) do not suppress the pituitary-adrenal system, (2) do not antagonize the peripheral effects of adrenal corticoids, and (3) do not block the hyperglycemic effects of glucagon and adrenalin."

(Presented before the Symposium on Endocrines and Nutrition, University of Michigan in Cooperation with National Vitamin Foundation, Ann Arbor, Oct. 11–12, 1956.)

Shoulder-Hand Syndrome

New York.—The need for experimental methods to reproduce the frequently mystifying shoulder-hand syndrome is emphasized by Otto Steinbrocker (Chief of Rheumatology Service, Hospital for Joint Diseases, New York).

Thus far, he reports, some work on smaller animals has been unrewarding, and the re-

quirement, less readily met, of studies in higher animals poses an obstacle in the search for causes of this phenomenon. But the direction thus indicated underscores Dr. Steinbrocker's observation that emotional factors in the brain or spinal cord merit serious consideration. He also cites the growing recognition of heart attacks in the etiology of reflex dystrophy, approaching in frequency the post-traumatic and idiopathic categories.

Dr. Steinbrocker stresses the importance of identifying the shoulder-hand syndrome in its earlier phases before trophic changes become irreversible. He reports good results in these stages through repeated blocks of the stellate ganglion with cortisone and/or corticotropin as second choice.

(Presented at the 50th Anniversary of the Hospital for Joint Diseases, New York, Nov. 15–17, 1956.)

Early Treatment Necessary for Orthopedic Conditions

New York.—The necessity for starting treatment very early in congenital dislocation of the hip, which calls for recognition of the condition in the earliest months of infancy, is strongly emphasized by Joseph E. Milgram (Director of Orthopedic Surgery, Hospital for Joint Diseases, New York). In this connection he cites the value of checking by roentgenogram on routine examination of the infant.

At the same time, Dr. Milgram notes that experience emphasizes the comparative fragility of the growing head of the thigh bone in the hip joint of the infant, and he cautions against injury to the dislocated head during replacement. The choice of the method of reduction in most early cases, he says, lies between essentially spontaneous replacement occurring during the course of gradual abduction (separation of the thighs) and reduction by gradual and increasing traction or pull downward on the limb itself. The choice of method of reduction is facilitated by roentgen-ray views made with the dislocated limb in various positions, while at times it is helpful to outline the joint with fluid that is opaque to roentgenograms. Open operation, he says, is a last resort in the very young.

(Presented at the 50th Anniversary of the Hospital for Joint Diseases, New York, Nov. 15–17, 1956.)

Aspirations of Joints

Holyoke, Mass.—Aspiration of joints as an office technique is reported on by David Goldberg (Holyoke Hospital). More than 2500 aspirations of the knee, ankle, elbow, and wrist joints have been performed during the past 15 years, he says, without a single infection.

He emphasized the simplicity of the method, without local anesthetic, easily removing the largest amount of fluid possible. By using this technique, he says, one need not hesitate to aspirate these joints as often as necessary for diagnostic and therapeutic purposes.

(Presented at the 50th Anniversary of the Hospital for Joint Diseases, New York, Nov. 15–17, 1956.)

New Aspects in the Treatment of Amenorrhea and Sterility

Copenhagen, Denmark.—Serum cholinesterase is inhibited by estrogens, reports Erik Christiansen (University of Copenhagen). He has used this observation to develop a method for determination of the blood estrogen variations in the menstrual cycle. Determinations can be carried out within an hour, while determination of estrogen excretion in the urine takes several days. Previously, amenorrhea was treated in his department with serum gonadotropin followed by chorionic gonadotropin after a fixed schedule. With the new method it is possible (1) to individualize the treatment by following the blood estrogen level, (2) to prevent overstimulation, and (3) to increase dosage until the right level has been reached.

One hundred and sixty-six patients have been treated; of 18 patients with primary amenorrhea, 9 began menstruation, 4 were found to be genetically masculine (negative

sex chromatin), and 3 had no ovaries. Of 148 with secondary amenorrhea, 134 began menstruation, of whom 119 had secretory and 14 proliferation (anovulatory) menses. The method is also used for evaluation of ovarian function in cases of sterility where no anatomic cause can be found. With the guidance of the blood estrogen determinations, gonadotropins were given to a number of patients successfully, Dr. Christiansen reports.

(Presented before the Danish Endocrinologic Society and Society for Gynecology and Obstetrics, Copenhagen, Denmark, Nov. 23, 1956.)

Effects of Ataraxics and Asphyxia in Cerebral Palsy

Chicago.—Studies of effects of ataractic agents in cerebral palsy showed that generally the drugs are not cure-alls, but through their tranquilizing effects they may be useful. Meprobamate, given to 53 children with pyramidal and extrapyramidal involvement, in dosages of 1.2 Gm. daily, gave better head control and more purposeful movements. In most cases the muscles felt less constricted to the examiner. Spasticity was reduced in 72 per cent. Poor emotional effects were noted in some patients.

Tests with zoxazolamine showed no significant change in spasticity or in range of motion. Sixty-seven children received 250 mg. tablets three times a day in the test. An additional 28 were given placebos.

Reserpine was shown to have no effect on improving the mean I.Q. test score and no effect on improving motor performance. It was shown that it does help in the alleviation of behavioral problems, especially in making the patient calmer and more relaxed, improving his general attitude, alertness, speech, social rapport, and attention span. It also has the tendency to make a few children happier and to decrease undesirable motor tics. Some of the undesirable side effects include stuffy nose, puffiness of the eyes, drowsiness, insomnia, negativism, and excessive drying.

A report of the Conference on Asphyxia Neonatorum, Brain Damage, and Impairment of Learning proves that asphyxia at birth produces neurologic deficits and impaired motor performance. The brains of guinea pigs asphyxiated for about eight minutes at birth and then resuscitated showed multiple small capillary hemorrhages. Some showed general neurologic damage and some just in specific areas of the brain. All animals demonstrated twitching and tremors, and most had inferior learning power.

(Presented before the American Academy for Cerebral Palsy, Chicago, Nov. 17–19, 1956.)

Cholesterol and Diabetes

Paris.—Insulin has a positive action in reduction of cholesterol, state R. Boulin and M. Gueniot (Paris) in discussing the problem of the relationship of cholesterol to diabetes. However, insulin does not suffice. In addition are needed medications that reduce cholesterolemia and special diet. Many investigators are studying the level of cholesterol and the severity of the diabetic state in conjunction, the authors continue, in order to determine if a parallel exists. The difficulty is how to determine when a diabetic state is "serious."

In case of a complication such as diabetic coma, they continue, there is often a great increase in the lipid level. However, there is no correlation between this high level and acidosis. Likewise, there is no correlation with arteritis of the lower members. The authors warn, in concluding, that in prescribing diets to diabetics, the tendency is, when cutting down on carbohydrates, to allow too many eggs and fats to be included. This is dangerous, they say. The diet must be well balanced.

As for use of medications with diabetics, the authors point out that insulin itself reduces the cholesterol level, in the long run. Medications such as hyposterol also have a long term positive effect.

(Presented before the French Society of Clinical Biology, Symposium on Cholesterol, Paris, Nov. 23–24, 1956.)

a new concept of medicine:

Stress

FIFTH ANNUAL REPORT 1955-1956

editors

HANS SELYE, M. D., Ph. D. (Prague), D. Sc. (McGill), F. R. S. (Canada), F. I. C. S. Professor and Director, Institut de Médicine et de Chirurgie expérimentales, University of Montreal.

GUNNAR HEUSER, M. D. (Cologne), Research Assistant and Librarian of the Institut de Médicine et de Chirurgie expérimentales, University of Montreal.

FOR THE CLINICIAN—new clinical perspectives in the treatment of diseases of adaptation.

FOR THE RESEARCH WORKER—a wealth of experimental data in biopathology and endocrinology.

FOR THE TEACHER—the most complete survey of the stress concept in modern medicine. In addition to Dr. Hans Selye's own original research work, special articles include:

special new articles

- PRIMARY ALDOSTERONISM, A NEW CLINICAL ENTITY by Jerome W. Conn and Lawrence H. Louis, University of Michigan.
- HORMONAL INFLUENCES ON INFLAMMATION AND DETOXIFICATION by T. F. Dougherty and R. D. Higginbotham, University of Utah.
- STRESS AND CATHECOL HORMONES by U. S. von Euler, Pysiologiska Institutionen, Stockholm, Sweden.
- ADRENAL INFLUENCES UPON THE STOMACH AND THE GASTRIC RESPONSE TO STRESS by S. J. Gray, G. Ramsey, R. Villareal and L. J. Krakauer, Peter Bent Brigham Hospital and Harvard Medical School.
- THE ROLE OF THE ADRENAL CORTEX IN THE ETIOLOGY OF DISEASE by D. J. Ingle, University of Chicago.
- ADRENOCORTICAL SECRETION AND FACTORS AFFECTING THAT SECRETION by D. H. Nelson, University of Utah.
- NEUROSECRETION by Ernst Scharrer, Albert Einstein College of Medicine, New York.
- SOME OBSERVATIONS ON PSYCHIATRIC STRESS IN INFANCY by R. A. Spitz, New York Psychoanalytic Institute.
- CORTISONE IN RELATION TO LYMPHOID TISSUE AND IMMUNITY by Herbert C. Stoerk, Merck Institute for Therapeutic Research.

A handsome, richly bound, fully illustrated volume of more than 800 pages, with a durable hard cover, at the price of $20.00.

MD *PUBLICATIONS, INC., 30 EAST 60th STREET, NEW YORK 22, N.Y.*

A new, essential, and timely book

ANTIBIOTICS ANNUAL 1956-1957

Edited by Henry Welch, Ph.D., and Félix Martí-Ibáñez, M.D.

Proceedings of the Fourth Annual Symposium on Antibiotics,
Washington, D. C., October 17, 18, and 19, 1956

155 REPORTS ON THE LATEST FINDINGS IN ANTIBIOTICS

by

390 AUTHORS REPRESENTING 12 COUNTRIES

Panel Discussions

- Antibiotics in Intestinal Antisepsis—Edwin J. Pulaski, Moderator
- Susceptibility of Microorganisms to Antibiotics Isolated from Hospitalized and Nonhospitalized Persons—W. A. Altemeier, Moderator
- Present Status of Antibiotics in the Preservation of Food—W. B. Rankin, Moderator

Some Selected Subjects Among the 155 Papers

- Further reports on the new antibiotic oleandomycin
- New novobiocin preparations
- The value of antibiotic combinations
- Complete descriptions of research on 4 new antibiotics: ristocetin, nucleocidin, alasopeptin, and PA 132
- A comparison of various antibiotic agents in pre- and postoperative therapy
- Continued clinical studies on vancomycin
- Latest uses of antibiotics in the preservation of foods
- The problems of synergism and resistance
- Newest indications for erythromycin therapy
- The local management of burns

ONLY $10.00 for a copy of this attractive, hardbound volume of over 1000 pages in length, including charts, illustrations, and a comprehensive index.

A Unique and Indispensable Volume for Every Physician, Research Worker, and Teacher

To order copies, write the publisher:

MEDICAL ENCYCLOPEDIA, INC., 30 East 60th Street, New York 22, N. Y.